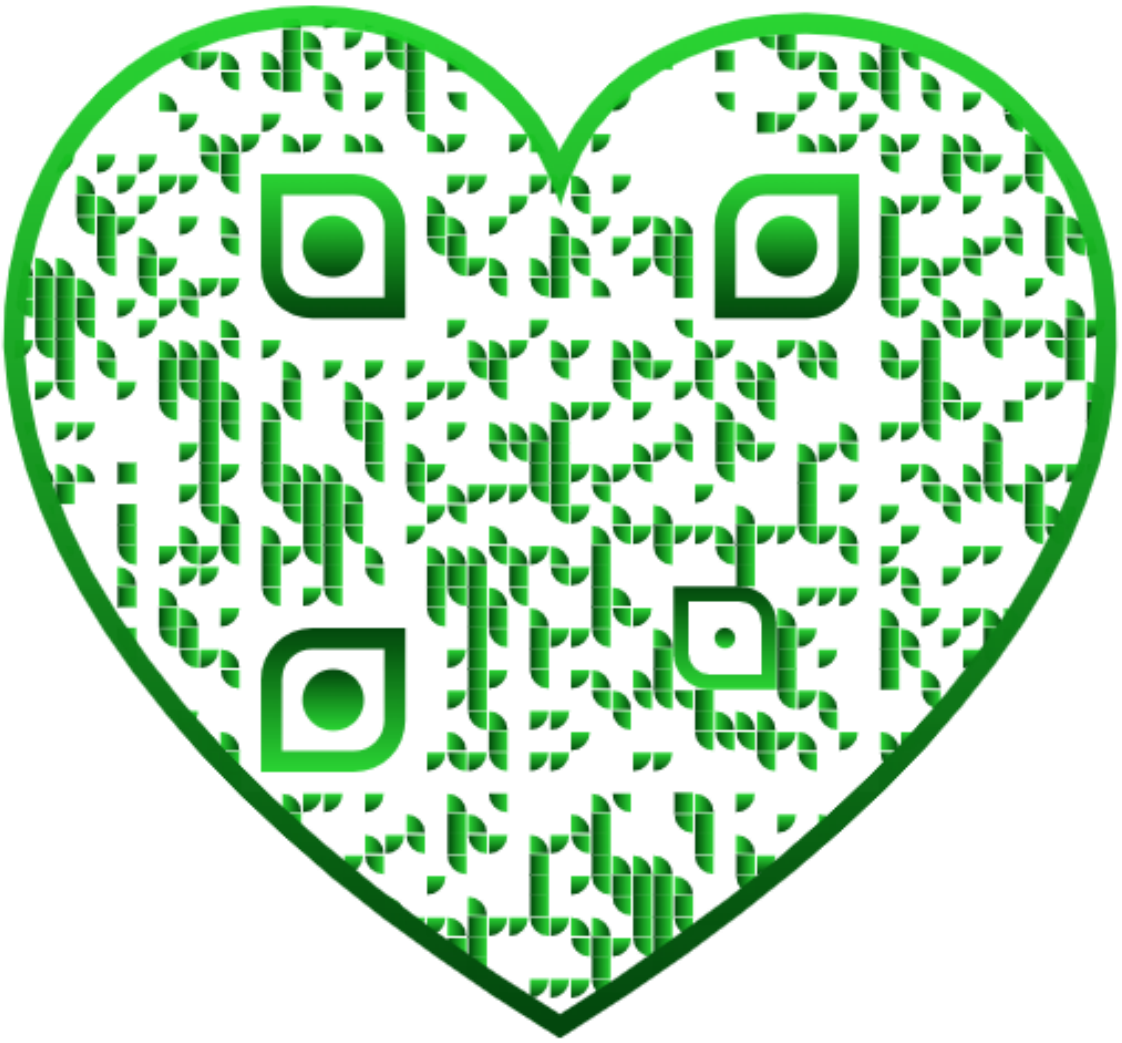
American College of Clinical Pharmacy

Updates in Therapeutics®:

Pharmacotherapy Preparatory Review and Recertification Course

2021 Edition
Volume 1



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Note: The authors and publisher of the Pharmacotherapy Preparatory Review and Recertification Course recognize that the development of this material offers many opportunities for error. Despite our very best efforts, some errors may persist into print. Drug dosage schedules are, we believe, accurate and in accordance with current standards. Readers are advised, however, to check other published sources to be certain that recommended dosages and contraindications are in agreement with those listed in this book. This is especially important in new, infrequently used, or highly toxic drugs.

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Errata: When possible, corrections to this publication are included in the 2021 Pharmacotherapy Preparatory Review and Recertification Course Errata, which will be available beginning May 17, 2021, at www.accp.com/media/ppc21/errata.pdf.

Continuing Pharmacy Education:
The American College of Clinical Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. The Universal Activity Numbers for the Pharmacotherapy Preparatory Review and Recertification Home Study Course, 2021 edition, are as follows: Pharmacokinetics: A Refresher, Men's and Women's Health, Pediatrics, and Policy, Practice, and Regulatory Issues, Activity No. 0217-0000-21-094-H04-P, 5.0 contact hours; Biostatistics: A Refresher, Study Designs, Chronic Care in Cardiology, and Acute Care in Cardiology, Activity No. 0217-9999-21-085-H04-P, 5.5 contact hours; Infectious Diseases I, Infectious Diseases II, Neurology, General Psychiatry, and Fluids, Electrolytes, and Nutrition, Activity No. 0217-9999-21-086-H01-P, 5.75 contact hours; Critical Care, Anticoagulation, Endocrine and Metabolic Disorders, Oncology Supportive Care, and Gastrointestinal Disorders, Activity No. 0217-9999-21-087-H01-P, 5.5 contact hours; Geriatrics, Nephrology, and Pulmonary Disorders and Adult Immunizations, Activity No. 0217-9999-21-088-H04-P, 3.5 contact hours. All Pharmacotherapy Preparatory Review and Recertification Course sessions are application-based activities.

To earn continuing pharmacy education credit for the home-study version of the 2021 Pharmacotherapy Preparatory Review and Recertification Course, you must review all content and complete the attestation statements and course evaluations by May 17, 2024. Statements of continuing pharmacy education credit will be available at CPE Monitor within 2–3 business days after completion of this activity.

Board Certified Pharmacotherapy Specialist (BCPS) Recertification Credit
The Pharmacotherapy Preparatory Review and Recertification Course is part of a Board of Pharmacy Specialties (BPS)-approved professional development program for BCPS recertification credit. To be eligible to earn the 25.25 contact hours of pharmacotherapy recertification credit for the Pharmacotherapy Preparatory Review and Recertification Course, you must purchase and successfully submit the completed web-based posttest(s) by 11:59 p.m. (CDT) on May 17, 2022. To learn more about the Board of Pharmacy Specialties (BPS) specialty exams, please visit their website: www.bpsweb.org.

The American College of Clinical Pharmacy (ACCP) has compiled the materials in this course book for pharmacists to use in preparing for the Board of Pharmacy Specialties (BPS) Pharmacotherapy Specialty certification examination. There is no intent or assurance that all of the knowledge on the examination will be covered in the ACCP process. Although ACCP does use the BPS Content Outline in creating the material for this course, ACCP does not know the specific content of any particular BPS examination. BPS guidelines prohibit any overlap of individuals writing the examination and developing preparatory materials. To maintain its strict, independent standards for certification, BPS does NOT endorse or provide review information, preparatory courses, or study guides for Board Certification Examinations.

Program Goals and Target Audience

The Updates in Therapeutics®: Pharmacotherapy Preparatory Review and Recertification Course is designed to help pharmacists who are preparing for the Board of Pharmacy Specialties certification examination in Pharmacotherapy as well as those seeking a general review and refresher on disease states and therapeutics. The program goals are as follows:

1. To present a high-quality, up-to-date overview of disease states and therapeutics;
2. To provide a framework to help attendees prepare for the specialty certification examination in pharmacotherapy; and
3. To offer participants an effective learning experience using a case-based approach with a strong focus on the thought processes needed to solve patient care problems in each therapeutic area.

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Updates in Therapeutics®:

Pharmacotherapy Preparatory Review and Recertification Course

Pharmacokinetics: A Refresher

Curtis L. Smith, Pharm.D., FCCP, BCPS

Ferris State University
Lansing, Michigan

Pharmacokinetics: A Refresher

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Learning Objectives

1. Identify and solve pharmacotherapy problems using basic pharmacokinetic concepts, including bioavailability, volume of distribution, clearance, and the elimination rate constant.
2. Describe clinically relevant issues related to drug transport proteins, cytochrome P450 metabolism, pharmacogenomics, and drug sampling and interpretation.
3. Describe specific pharmacokinetic characteristics and target concentrations of commonly used therapeutic agents, including aminoglycosides, vancomycin, phenytoin, valproic acid, and digoxin, as well as pharmacokinetic alterations in patients with renal and hepatic disease.

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. J.H., a 65-year-old woman (weight 65 kg), was recently initiated on tobramycin and piperacillin/tazobactam for the treatment of hospital-acquired pneumonia. After the first tobramycin dose of 120 mg (infused from noon to 1:00 p.m.), serum tobramycin concentrations are obtained. They are 4.4 mg/L at 3:00 p.m. and 1.2 mg/L at 7:00 p.m. Which is the best assessment regarding the calculation of tobramycin pharmacokinetic parameters in this patient?
   A. Data are sufficient to determine the half-life but not the volume of distribution (Vd).
   B. Data are sufficient to determine both the half-life and the Vd.
   C. Data are insufficient to determine either the half-life or the Vd.
   D. Data are sufficient to determine the Vd but not the half-life.

2. P.L. is a 60-year-old woman (60 kg) recently initiated on gentamicin and clindamycin. After the first gentamicin dose of 110 mg (infused from 6:00 p.m. to 6:30 p.m.), serum gentamicin concentrations are obtained. They are 3.6 mg/L at 7:30 p.m. and 0.9 mg/L at 11:30 p.m. Which is the best assessment of this patient's gentamicin pharmacokinetic parameters?
   A. The half-life is about 2 hours.
   B. The half-life is about 3 hours.
   C. The maximum concentration (Cmax) is about 3.8 mg/L.
   D. The Vd is about 11.6 L.

3. R.O. is a 74-year-old woman initiated on gentamicin 100 mg intravenously every 24 hours for pyelonephritis. On admission, her serum creatinine (SCr) is 1.8 mg/dL. She has heart failure and is fluid overloaded because of her diminished renal function, and she is nonadherent to her angiotensin-converting enzyme inhibitor and diuretic. A few days into her hospitalization, her SCr is down to 1.1 mg/dL, and she is reinitiated on furosemide and enalapril. Which most likely happened to the gentamicin half-life in R.O. during her hospitalization?
   A. Her clearance increased, which increased her Vd and decreased her half-life.
   B. Her clearance increased, which increased her elimination rate constant and decreased her half-life.
   C. Her Vd decreased, which increased her clearance and decreased her half-life.
   D. Her Vd decreased, which increased her elimination rate constant and increased her half-life.

4. A patient receives vancomycin 1000 mg intravenously every 24 hours and has a trough concentration, obtained 30 minutes before the next dose, of 6 mg/L, with an estimated vancomycin 24-hour AUC of 210 mg * hour/L. Which regimen is best for this patient if the goal AUC/MIC is 400–600 (assuming an MIC of 1 mg/L)?
   A. Maintain the dosage at 1000 mg intravenously every 24 hours.
   B. Lower the dosage to 500 mg but keep the interval at every 24 hours.
   C. Keep the dosage at 1000 mg but shorten the interval to every 12 hours.
   D. Lower the dosage to 500 mg and shorten the interval to every 12 hours.

5. R.K., a 39-year-old man who is HIV positive, receives a diagnosis of cryptococcal meningitis and begins taking amphotericin B and flucytosine.

You want to keep flucytosine peak concentrations at 50–100 mcg/mL. Assuming a steady-state trough concentration of 25 mcg/mL, dosing every 6 hours, and 100% bioavailability, which is the best dosage to achieve a peak concentration within the desired range (flucytosine volume of distribution of 0.7 L/kg and half-life of 3 hours)?

A. 12.5 mg/kg.

B. 37.5 mg/kg.

C. 75 mg/kg.

D. 150 mg/kg.

6. L.R. is a 49-year-old patient with diabetes mellitus and renal failure. He was recently in a car accident and sustained a head trauma. He currently receives phenytoin 100 mg intravenously three times a day, and his most recent concentration was 5.6 mcg/mL. You are asked to suggest a new dosage to achieve a concentration within the therapeutic range. Laboratory results include sodium 145 mEq/L, potassium 3.9 mEq/L, chloride 101 mEq/L, carbon dioxide 26 mEq/L, blood urea nitrogen (BUN) 95 mg/dL, SCr 5.4 mg/dL, glucose 230 mg/dL, and albumin (Alb) 2.8 g/dL. Which is the best recommendation?

   A. Increase the dosage to 200 mg intravenously three times a day.

   B. Increase the dosage to 200 mg intravenously two times a day.

   C. Decrease the dosage to 100 mg intravenously two times a day.

   D. Keep the dosage the same.

7. You are asked how the fluorescence polarization immunoassay (TDx) and enzyme multiplied immunoassay technique (EMIT) assays compare with each other. Which statement is most accurate?

   A. Although both are immunoassays, one uses antibodies to bind the molecule of interest, whereas the other uses antigens.

   B. Although both are immunoassays, one uses an enzyme label, whereas the other uses a radioisotope label.

   C. Although both are immunoassays, one uses an enzyme label, whereas the other uses a fluorescent label.

   D. They are both names for the same assay technique.

8. An older adult is seen in the morning medicine clinic for a routine follow-up. Medication history includes digoxin 0.25 mg/day by mouth, furosemide 40 mg/day by mouth, and potassium chloride 10 mEq/day by mouth. All doses were last taken at 8:00 a.m. today at home. The patient has vague complaints of stomach upset, which began 2 days ago, but is otherwise in no apparent distress. A serum digoxin concentration obtained today at 10:00 a.m. is 2.5 mcg/L. Which statement best describes what should be done next?

   A. Admit the patient for administration of digoxin Fab.

   B. Tell the patient to skip tomorrow's dose of digoxin and begin 0.125 mg/day by mouth.

   C. Administer a dose of activated charcoal.

   D. Do nothing today with the digoxin.

9. A research group is analyzing the relationship between various independent patient demographics (e.g., age, height, weight, albumin, creatinine clearance [CrCl]) and phenytoin pharmacokinetics. Which is the best statistical test to use in assessing the relationship?

   A. One-way analysis of variance.

   B. Analysis of covariance.

   C. Multiple regression.

   D. Spearman rank correlation.

10. N.T. is a 24-year-old woman receiving valproic acid for tonic-clonic seizures. Her most recent trough valproic acid concentration was 22 mg/L. Her most recent albumin concentration was 4.1 g/dL. Given this albumin, which recommendation is best regarding her dosage?

    A. Continue with the current dosage; the concentration is close enough to the therapeutic range.

    B. Assess adherence and increase her dosage; the concentration is below the therapeutic range.

    C. Decrease her dosage; the concentration is slightly above the therapeutic range.

    D. Assess adherence and then check a free valproic acid concentration and adjust accordingly.

11. N.G. is a 54-year-old woman with a recent head injury. She comes to your pharmacy with complaints about the prescription for acetaminophen with codeine you dispensed to her yesterday. She says that it does not seem any stronger than when she uses acetaminophen alone. On her profile, you notice results from pharmacogenomics testing performed 3 years ago that shows she is a CYP2D6 poor metabolizer. In addition to acetaminophen and codeine, she is receiving aspirin, clopidogrel, omeprazole, lisinopril, citalopram, metoprolol succinate, docusate, and trazodone. Which is the best explanation why N.G. does not seem to benefit from codeine?
    A. Omeprazole inhibited CYP2C19, causing less codeine activation.
    B. Codeine is not as active in N.G. because of her genetic profile.
    C. Codeine is metabolized faster in N.G., leading to lower concentrations.
    D. Metoprolol inhibited CYP2C9, causing less codeine activation.

12. At your hospital you are responsible for making dosing adjustments in patients with poor renal function. While working with you, a student asks why you are using the Cockcroft-Gault method for estimating CrCl instead of the newer Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equations. Which is the best response to provide to this student?
    A. MDRD and CKD-Epi are not as good estimates of renal function and may lead to inappropriate changes in drug dosing.
    B. MDRD and CKD-Epi were developed in an ambulatory care population and cannot be used for hospitalized patients.
    C. The Cockcroft-Gault estimate of CrCl has units that are different from the glomerular filtration rate estimates calculated using the MDRD and CKD-Epi equations.
    D. Recommendations for renal dosing adjustments in package inserts are usually based on CrCl estimates using the Cockcroft-Gault equation.

13. An assay used for therapeutic drug monitoring at your institution has a low sensitivity and low precision. Which is the best statement about the impact of this assay on drug monitoring?
    A. The assay may be unable to detect concentrations that are therapeutic, and it will report highly variable values when repeatedly run on the same sample.
    B. The assay may be unable to detect concentrations that are therapeutic, and it will consistently over- or under-measure the true concentration.
    C. The assay will be unable to differentiate between like substances, and it will consistently over- or under-measure the true concentration.
    D. The assay will be unable to differentiate between like substances, and it will report highly variable values when repeatedly run on the same sample.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain I: Patient-Centered Pharmacotherapy
    a. Task 1: Knowledge statements: 1-7, 11, 12.
    b. Task 4: Knowledge statements: 2, 3, 5, 6.
2. Domain II: Drug Information and Evidence-Based Medicine
    a. Task 3: Knowledge statements: 4.

Patient Cases

1. H.R. is receiving vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia. H.R. has chronic kidney disease. A 1-g intravenous dose of vancomycin is given at noon on March 21. A concentration obtained at 2:00 p.m. on March 21 is 27.8 mcg/mL. After no additional doses, a concentration obtained at 2:00 p.m. on March 24 is 14.1 mcg/mL. If you were to give a 1-g dose at 4:00 p.m. on March 24 and your goal trough concentration to achieve an appropriate AUC/MIC ratio was 10–15 mg/L, which would be the best time to give the next dose?
   A. 1 day after the dose on the 24th.
   B. 3 days from the dose on the 24th.
   C. 6 days from the dose on the 24th.
   D. Insufficient information to calculate when to redose.

2. After the administration of 100 mg of a drug intravenously and 200 mg of the same drug by mouth, the areas under the curves (AUCs) are 50 and 25 mg/L/hour, respectively. Which best describes the bioavailability of this drug?
   A. 25%.
   B. 37.5%.
   C. 50%.
   D. 100%.

I. BASIC PHARMACOKINETIC RELATIONSHIPS

Table 1 contains definitions of terms.

Table 1. Pharmacokinetic Term Definitions

AUC	Area under the curve
AUC_{ev}	Area under the curve after an extravascular dose
AUC_{iv}	Area under the curve after an intravenous dose
Cmax	Maximum concentration
Cmin	Minimum concentration
C_0	Concentration at time zero
C_{ss}	Concentration at steady state
$C_{ss\ avg}$	Average concentration at steady state
$C_{ss\ max}$	Maximum concentration at steady state
$Dose_{EV}$	Dose given extravascularly
$Dose_{IV}$	Dose given intravenously
F	Bioavailability
k	Elimination rate constant
R_0	Rate of infusion
τ	Dosing interval
t	Time of the intermittent infusion
t_i	Time from initiation of the continuous infusion
Vd	Volume of distribution

A. Absorption $F = \frac{dose_{iv} * AUC_{ev}}{dose_{ev} * AUC_{iv}}$

B. Distribution

Rapid intravenous (or oral) bolus: $Vd = \frac{F * dose}{C_0}$

Continuous intravenous infusion at steady state: $Vd = \frac{R_0}{k * C_{ss}}$

Continuous intravenous infusion before steady state: $Vd = \frac{R_0}{C * k}(1-e^{-kt_i})$ and $C = \frac{R_0}{V_d * k}(1-e^{-kt_i})$

Multiple intravenous bolus at steady state: $Vd = \frac{dose}{C_{ss\,max} * (1-e^{-k\tau})}$

Multiple intermittent intravenous infusion at steady state: $Vd = \frac{R_0}{k} * \frac{1-e^{-kt}}{C_{max} - (C_{min} * e^{-kt})}$

$C_{ss\,max} = \frac{R_0 * (1-e^{-kt})}{V_d * k * (1-e^{-kt})}$ $C_{ss\,min} = C_{ss\,max} * e^{-k(\tau - t)}$

C. Clearance

$Clearance = \frac{dose}{AUC}$ $k = \frac{Cl}{V_d}$ $k = \frac{(1nC_1 - 1nC_2)}{(t_2 - t_1)}$ $t_{1/2} = \frac{0.693}{k}$

Continuous intravenous infusion at steady state: $Clearance = \frac{R_0}{C_{ss}}$

Continuous intravenous infusion before steady state: $Clearance = \frac{R_0}{C} * (1 - e^{-kt_i})$

Multiple intravenous (or oral) bolus at steady state: $Clearance = \frac{\frac{F*dose}{\tau}}{C_{ss,avg}}$

$\tau = \frac{(1nC_{max} - 1nC_{min})}{k}$

II. ABSORPTION

A. First-Pass Effect

1. Blood that perfuses almost all the gastrointestinal (GI) tissues passes through the liver by means of the hepatic portal vein.
   a. Fifty percent of the rectal blood supply bypasses the liver (middle and inferior hemorrhoidal veins).
   b. Drugs absorbed in the buccal cavity bypass the liver.

2. Examples of drugs with significant first-pass effect

Amitriptyline	Isosorbide dinitrate	Nicardipine	Propranolol
Desipramine	Labetalol	Nifedipine	Verapamil
Diltiazem	Lidocaine	Nitroglycerin	
Doxepin	Metoprolol	Pentazocine	
Imipramine	Morphine	Propoxyphene	

B. Enterohepatic Recirculation (Table 2)
   1. Drugs are excreted through the bile into the duodenum, metabolized by the normal flora in the GI tract, and reabsorbed into the portal circulation.
   2. Occurs with drugs that have biliary (hepatic) elimination and good oral absorption
   3. Drug is concentrated in the gallbladder and expelled on sight, smell, or ingestion of food.

Table 2. Examples of Compounds Excreted in Bile and Subject to Enterohepatic Cycling

Compound	Entity in Bile
Chloramphenicol	Glucuronide conjugate
Digoxin	Parent
Estrogens	Parent
Imipramine	Parent and desmethyl metabolite
Indomethacin	Parent and glucuronide
Nafcillin	Parent
Rifampin	Parent
Sulindac	Glucuronides of parent and metabolites
Testosterone	Conjugates
Tiagabine	Glucuronide conjugate
Valproic acid	Glucuronide conjugates
Vitamin A	Conjugates

Patient Case

3. Which statement best describes P-glycoprotein?
   A. It is a plasma protein that binds basic drugs.
   B. It transfers drugs through the GI mucosa, increasing absorption.
   C. It diminishes the effect of cytochrome P450 3A4 (CYP3A4) in the GI mucosa.
   D. It is an efflux pump that decreases GI mucosal absorption.

C. P-Glycoprotein
   1. P-glycoprotein is an efflux pump (located in the esophagus, stomach, and small and large intestines) that pumps drugs back into the GI lumen; it is a more important factor in drug interactions during drug absorption than intestinal CYP3A4.
   2. Both CYP3A4 and P-glycoprotein are located in small intestinal enterocytes and work together to decrease the absorption of xenobiotics.
   3. Most CYP3A4 substrates are also P-glycoprotein substrates.
   4. Many CYP3A4 inhibitors/inducers also inhibit/induce P-glycoprotein, leading to an increase or decrease in bioavailability.

5. Examples of P-glycoprotein absorption drug interactions
    a. Dabigatran is affected by rifampin, St. John's wort, quinidine, ketoconazole, verapamil, amiodarone, and dronedarone.
    b. Digoxin is affected by St. John's wort, quinidine, verapamil, amiodarone, and dronedarone or dabigatran.
    c. Human immunodeficiency virus protease inhibitors are affected by rifampin, St. John's wort, and hepatitis C direct-acting antivirals.

III. DISTRIBUTION

A. Definition: Apparent Vd: Proportionality constant that relates the amount of drug in the body to an observed concentration of drug

B. Protein Binding (Table 3)

Table 3. Common Proteins Involved in Drug Protein Binding

Protein	Types of Drugs Bound	Molecular Weight	Normal Concentrations	
			g/L	mcmol
Albumin	Acidic	65,000	35–50	500–700
α-1-Acid glycoprotein	Basic	44,000	0.4–1.0	9–23
Lipoprotein	Lipophilic and basic	200,000–3,400,000	Variable	Variable

C. P-Glycoprotein
1. Functions as an efflux pump on the luminal surface of the blood-brain barrier, limiting entry to the central nervous system
2. It may be especially important with opioids: Induction of P-glycoprotein by chronic use of opioids may decrease the opioid effect (tolerance).
3. P-glycoprotein is also found in tumor cells, resulting in the efflux of chemotherapeutic agents from the cell and, ultimately, multidrug resistance.

IV. CLEARANCE

A. Metabolic enzymes (Table 4) and transport proteins (Table 5) involved in drug clearance

Table 4. Enzymes Involved in Drug Metabolism

Oxygenases CYPs Monoamine oxygenases Alcohol dehydrogenases Aldehyde dehydrogenases Xanthine dehydrogenases	**Hydrolytic enzymes** Esterases Amidases Epoxide hydrolases Dipeptidases
Conjugating enzymes Uridine diphosphate–glucuronyl transferases Glutathione *S*-transferase Acetyltransferases Methyltransferases	

CYP = cytochrome P450.

Table 5. Drug Transport Proteins

Transport Protein Superfamily	Transport Protein (Gene [Protein])	Location and Function	Drugs Affected by Transport Protein	Inhibitors of Transport Protein
SLC	*SLC01A2* [OATP1A2]	Hepatocyte: Bile acid uptake	Digoxin Levofloxacin Methotrexate Statins	Naringin
	SLCO1B1 [OATP1B1]	Hepatocyte: Hepatic uptake of drugs	Hepatitis C direct-acting antivirals Pravastatin Rifampin Simvastatin Valsartan	Clarithromycin Cyclosporine Gemfibrozil Hepatitis C direct-acting antivirals
	SLCO1B3 [OATP1B3]	Hepatocyte: Hepatic uptake of drugs	Digoxin Fexofenadine Rifampin Statins	Cyclosporine Erythromycin
	SLC22A1, SLC22A2, SLC22A6, SLC22A8 [OAT and OCT]	Hepatocyte: Hepatic uptake of drugs Renal tubule (interstitial side): Secretion of drugs	Dofetilide[b] Methotrexate[a] Organic anions and cations[b] Salicylate[a] Tetracycline[a] Zidovudine[a]	Cimetidine
	SLCO2B1 [OATP2B1]	Hepatocyte: Hepatic uptake of drugs	Fexofenadine Glyburide Statins	Cyclosporine Gemfibrozil
	SLC15A1, SLC15A2 [PEPT1, PEPT2]	Renal tubule Intestinal enterocytes	Captopril Cephalexin Enalapril Valacyclovir	
	SLC47A1, SLC47A2 [MATE1, MATE2-K]	Renal tubule	Metformin	Cimetidine
ABC	*ABCB11* [BSEP]	Hepatocyte: Bile acid excretion into bile	Pravastatin	
	ABCC2, 3, 4, and *5* [MRP2, 3, 4, and 5]	Hepatocyte: Excreting water-soluble drugs and metabolites into blood Renal tubule (luminal side): Secretion of drugs	Glucuronide, sulfate, and glutathione metabolites[a] Methotrexate[a] Pravastatin[a] Rifampin[a]	Probenecid Ritonavir
	ABCB1 [MDR1] (P-glycoprotein)	Hepatocyte: See text in handout Renal tubule (luminal side): See text in handout	See text	Amiodarone Quinidine Verapamil
	ABCB4 [MDR3]	Hepatocyte	Digoxin Paclitaxel Vinblastine	Itraconazole Ritonavir
	ABCG2 [BCRP]	Hepatocyte: Biliary excretion	Daunorubicin Doxorubicin Imatinib Methotrexate Mitoxantrone Statins Topotecan	Omeprazole Ritonavir

[a]Drugs affected by transport proteins in hepatocytes.

[b]Drugs affected by transport proteins in the renal tubule.

Patient Case

4. A renal transplant patient receiving cyclosporine is given a diagnosis of community-acquired pneumonia. The patient is admitted to the hospital and initiated on ceftriaxone and a macrolide. A physician asks you to choose a macrolide that will not interact with the patient's cyclosporine. Which macrolide is the best choice to meet the physician's criteria?

   A. Erythromycin.

   B. Clarithromycin.

   C. Azithromycin.

   D. Any macrolide (all macrolides inhibit CYP3A4).

B. Cytochrome P450

1. Introduction

   a. A group of heme-containing enzymes responsible for phase 1 metabolic reactions

   b. Characteristic absorbance of light at 450 nm (hence CYP450)

   c. Located primarily in the membranes of the smooth endoplasmic reticulum in the liver, small intestine, brain, lung, and kidney

   d. Encoded by a supergene family and subfamily; separate genes code for different isoenzymes

   e. Drugs generally have a high affinity for one particular CYP, but most drugs also have secondary pathways (see Table 6).

Table 6. CYP Drug Interactions

Gene Designation	CYP1A2	CYP2C9/10	CYP2C19	CYP2D6	CYP3A4	
Induction	Carbamazepine Modafinil Nafcillin Omeprazole Rifampin	Enzalutamide Phenobarbital Phenytoin Rifampin Rifapentine	Carbamazepine Efavirenz Enzalutamide Phenobarbital Prednisone Rifampin St. John's wort		Carbamazepine Efavirenz Enzalutamide Modafinil Nevirapine Oxcarbazepine Phenobarbital Phenytoin	Pioglitazone Rifabutin Rifampin Rifapentine St. John's wort
Inhibition	Amiodarone Cimetidine Ciprofloxacin Diltiazem Efavirenz Erythromycin Fluvoxamine Mexiletine Norfloxacin	Amiodarone Efavirenz Fenofibrate Fluconazole Fluvoxamine Isoniazid Lovastatin Metronidazole Paroxetine Sertraline Sulfamethoxazole Trimethoprim Voriconazole	Cimetidine Esomeprazole Fluoxetine Fluvoxamine Isoniazid Ketoconazole Lansoprazole Modafinil Omeprazole Oxcarbazepine Pantoprazole Topiramate Voriconazole	Amiodarone Bupropion Celecoxib Chlorpheniramine Cimetidine Cinacalcet Citalopram Diphenhydramine Duloxetine Escitalopram Fluoxetine Haloperidol Methadone Metoclopramide Midodrine Paroxetine Propafenone Quinidine Ritonavir Sertraline Terbinafine Thioridazine	Amiodarone Aprepitant Atazanavir Boceprevir Cimetidine Clarithromycin Darunavir Delavirdine Diltiazem Erythromycin Fluconazole (large doses)	Fluvoxamine Fosamprenavir Imatinib Itraconazole Ketoconazole Nelfinavir Ritonavir Suboxone Telaprevir Verapamil Voriconazole

Table 6. CYP Drug Interactions *(Cont'd)*

Gene Designation	CYP1A2	CYP2C9/10	CYP2C19	CYP2D6	CYP3A4	
Substrates	Acetaminophen Amitriptyline Caffeine Clomipramine Clozapine Cyclobenzaprine Estradiol Fluvoxamine Haloperidol Imipramine Mirtazapine Olanzapine Riluzole Ropinirole *R*-warfarin Theophylline Zolmitriptan	Amitriptyline Celecoxib Diclofenac Fluoxetine Glimepiride Glipizide Glyburide Ibuprofen Indomethacin Irbesartan Losartan Phenytoin Rosuvastatin *S*-warfarin Tamoxifen	Amitriptyline Cilostazol Citalopram Clomipramine Clopidogrel Diazepam Imipramine Lansoprazole Naproxen Omeprazole Pantoprazole Phenobarbital Phenytoin Propranolol	Amitriptyline Aripiprazole Atomoxetine Carvedilol Clomipramine Clozapine Codeine Dextromethorphan Donepezil Duloxetine Flecainide Fluoxetine Fluvoxamine Haloperidol Hydrocodone Imipramine Metoprolol Mirtazapine Nebivolol Nortriptyline Oxycodone Paroxetine Propafenone Propranolol Risperidone Tamoxifen Thioridazine Timolol Tramadol Trazodone Venlafaxine	Alprazolam Amiodarone Amlodipine Aprepitant Aripiprazole Atorvastatin Boceprevir Buspirone Carbamazepine Cilostazol Citalopram Clarithromycin Cyclosporine Dapsone Darunavir Delavirdine Diazepam Diltiazem Donepezil Efavirenz Eplerenone Erlotinib Erythromycin Ethinyl estradiol Felodipine Fentanyl Finasteride Fosamprenavir Gefitinib Imatinib Irinotecan Itraconazole Ketoconazole Lapatinib Lidocaine	Lovastatin Methadone Midazolam Mirtazapine Nateglinide Nevirapine Nifedipine Quetiapine Quinidine Repaglinide Rifabutin Ritonavir Sertraline Sibutramine Sildenafil Simvastatin Sirolimus Sorafenib Sunitinib Tacrolimus Telaprevir TCAs (amitriptyline, clomipramine, imipramine) Tiagabine Trazodone Triazolam Vardenafil Verapamil Voriconazole Zaleplon Ziprasidone Zolpidem Zonisamide

f. Nomenclature

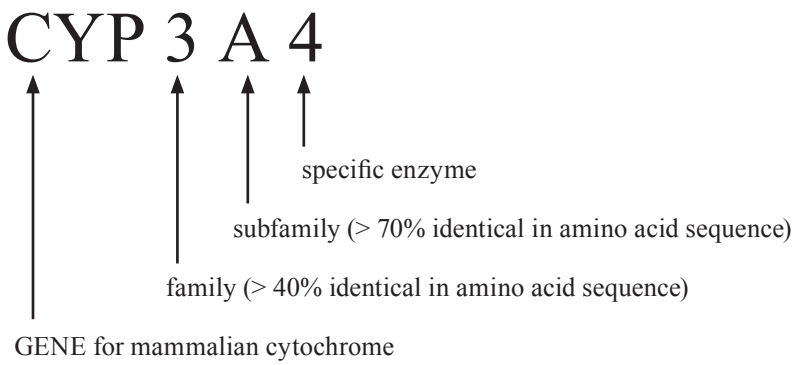
CYP 3 A 4
specific enzyme
subfamily (> 70% identical in amino acid sequence)
family (> 40% identical in amino acid sequence)
GENE for mammalian cytochrome

Figure 1. Nomenclature.

2. Distribution of CYP isoenzymes in human liver

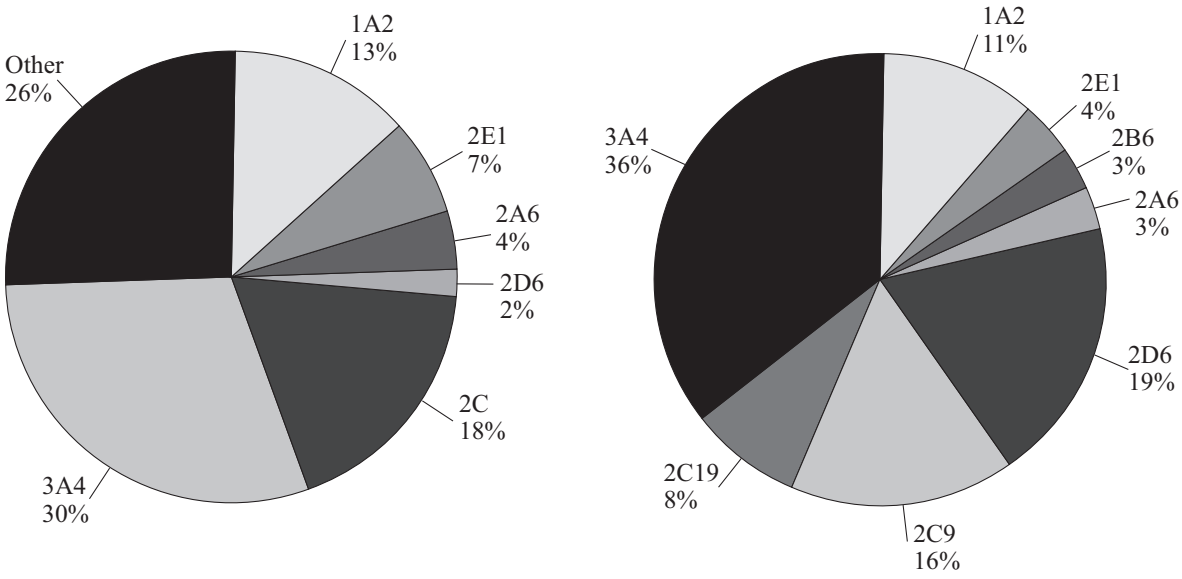

Figure 2. Distribution of CYP isoenzymes in human liver.

3. Distribution of CYP isoenzymes in human GI tract

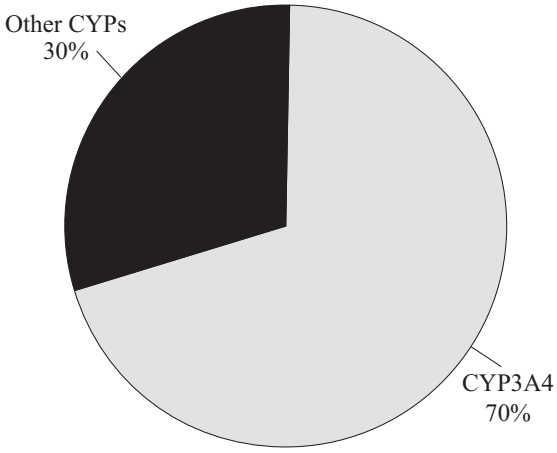

Figure 3. Distribution of CYP isoenzymes in human gastrointestinal tract.

4. Characteristics of CYP metabolism
   a. Inhibition is substrate-independent.
   b. Some substrates are metabolized by more than one CYP (e.g., tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs]).
   c. Enantiomers may be metabolized by different CYP isoenzymes (e.g., R- vs. S-warfarin).
   d. Differences in inhibition may exist in the same class of agents (e.g., fluoroquinolones, azole antifungals, macrolides, calcium channel blockers, histamine-2 blockers).
   e. Substrates can also be inhibitors (e.g., erythromycin, verapamil, diltiazem).

f. Most inducers and some inhibitors can affect more than one isozyme (e.g., cimetidine, ritonavir, fluoxetine, erythromycin).
g. Inhibitors may affect different isozymes at different dosages (e.g., fluconazole inhibits CYP2C9 at dosages of 100 mg/day or greater and inhibits CYP3A4 at dosages of 400 mg/day or greater).

5. Drug interactions
   a. Induction – Adaptive increase in enzyme activity in response to another agent – Slow, regulatory process
      i. Induction is dose-dependent.
      ii. Onset – Usually begins after several days, with a maximal effect within 2 weeks (somewhat dependent on the potency and half-life of the inducer)
      iii. Offset – Usually longer to eliminate enzymes than to generate enzymes; enzyme activity returns to normal within 2–3 weeks (somewhat dependent on the half-life of the inducer)
   b. Inhibition – Direct action on an enzyme that renders the enzyme inactive
      i. Inhibition is dose-dependent.
      ii. Onset – Quicker than induction (inhibition begins as soon as the inhibiting agent is in the system), but dependent on the half-life of the inhibiting agent and the substrate (i.e., time to steady state for both agents)
      iii. Offset – Effect is gone as soon as the inhibiting agent is eliminated.

C. P-Glycoprotein
   1. P-glycoprotein is an efflux pump that pumps drugs into the bile; the clinical effect of P-glycoprotein drug interactions in the bile is unknown.
   2. P-glycoprotein pumps drugs from renal tubules into the urine; it also potentially limits the degree of reabsorption.
   3. Examples of drug interactions: quinidine/digoxin, cyclosporine/digoxin, and propafenone/digoxin

Patient Case

5. W.T., a 62-year-old man who presents to the emergency department with chest pain, is given a diagnosis of a non-ST-segment elevation myocardial infarction. He goes to the catheterization laboratory, where two drug-eluting stents are placed. After stent placement, he is initiated on aspirin 81 mg daily and clopidogrel 75 mg daily. A CYP2C19 pharmacogenetic test shows that he is a poor metabolizer (*CYP2C19*3/*3* genotype). The patient also receives losartan 25 mg daily, carvedilol 25 mg twice daily, amitriptyline 100 mg daily, acetaminophen 500 mg as needed, and simvastatin 20 mg daily. Given his pharmacogenetic profile, which is most likely to occur in this patient?

   A. He will form a metabolite of clopidogrel that will block the action of aspirin, increasing the risk of a thrombotic event.
   B. He will not activate clopidogrel well, increasing the risk of a thrombotic event.
   C. He will not metabolize clopidogrel well, increasing the risk of a bleeding event.
   D. He will overproduce an active metabolite of clopidogrel, increasing the risk of a bleeding event.

D. Pharmacogenomics and Pharmacogenetics
   1. Population in general is divided into poor, intermediate, extensive, and ultrarapid metabolizers; therefore, metabolism is considered polymorphic.
   2. Definition of polymorphism: Coexistence of more than one genetic variant (alleles), which are stable components in the population (more than 1% of population)
   3. Clear antimode (separation between the two populations) results

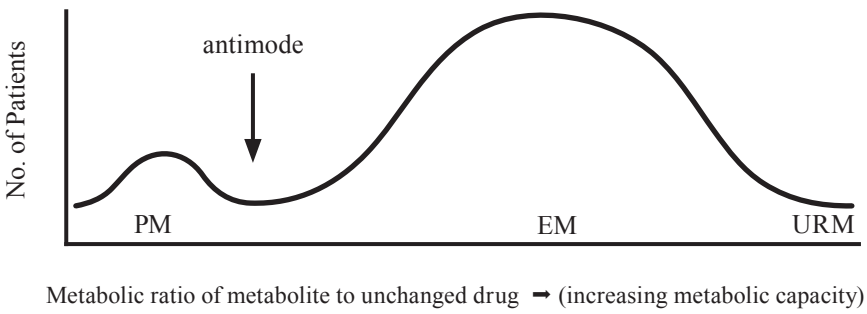

Figure 4. Distribution of patients in a drug that follows polymorphic metabolism.
EM = extensive metabolizer; PM = poor metabolizer; URM = ultrarapid metabolizer.

4. Phenotype: Expression of the trait; interaction of gene with environment
   a. Manifestation of the trait clinically
   b. Not necessarily constant
5. Genotype: Genetic makeup
6. Pharmacogenomics in clinical practice (Table 7)

Table 7. Pharmacogenetics in Drug Metabolism, Drug Transport, Drug Target, and Adverse Drug Reactions

Type	Enzyme/Target	Most Common Variant Alleles	Drug Examples
Drug metabolism	*CYP2C9*	*CYP2C9*2 (70%–90% activity)* *CYP2C9*3 (10%–30% activity)*	NSAIDs Phenytoin Warfarin
Drug metabolism	*CYP2C19*	*CYP2C19*2 (poor)* *CYP2C19*3 (poor)* *CYP2C19*17 (ultrarapid)* *CYP2C19*4 (null variant)*	Clopidogrel Diazepam Omeprazole SSRIs Tricyclic antidepressants Voriconazole
Drug metabolism	*CYP2D6*	*CYP2D6*10 (poor)* *CYP2D6*17 (poor)* *CYP2D6*3, *4, and *5 (null)*	Antiarrhythmics Antipsychotics Beta blockers Codeine, hydrocodone, oxycodone Dextromethorphan SSRIs Tamoxifen Tramadol Tricyclic antidepressants
Drug metabolism	*UDP-glucuronosyltransferases*	*UGT1A1*6* *UGT1A1*28* *UGT2B7*2* *UGT2B7*28*	Atazanavir Irinotecan Mycophenolate NSAIDs
Drug metabolism	*N*-acetyltransferase	*NAT2*4* *NAT2*5* *NAT2*6* *NAT2*7*	Hydralazine Isoniazid Sulfasalazine

Table 7. Pharmacogenetics in Drug Metabolism, Drug Transport, Drug Target, and Adverse Drug Reactions *(Cont'd)*

Type	Enzyme/Target	Most Common Variant Alleles	Drug Examples
Drug transport	*SLCO1B1*	*SLCO1B1*1A,*1B* *SLCO1B1*5, *15, *17*	Simvastatin
Drug target	*VKOR*	*VKORC1*2 (increases)* *VKORC1*3 (decreases)*	Warfarin
Adverse drug reactions	*HLA-B*	*HLA-B*5701*	Abacavir
		*HLA-B*5801*	Allopurinol
		*HLA-B*1502*	Carbamazepine, phenytoin

NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor.

6. Clinical Pharmacogenetics Implementation Consortium (CPIC)
   a. Designed to facilitate translation of pharmacogenetics information from research to clinical practice
   b. Developing guidelines for use of pharmacogenetic test results in drug dosing
   c. Focused on specific drug-gene pairs (Table 8)

Table 8. CPIC Clinical Recommendations for Drug-Gene Pairs

Drug	Gene	Recommendation
Abacavir	*HLA-B*	Avoid using because of increased incidence of hypersensitivity reactions in patients with the *HLA-B*57:01* allele
Allopurinol	*HLA-B*	Severe cutaneous adverse reactions associated with carriers of the *HLA-B*58:01* allele Avoid using allopurinol in these patients
Atazanavir	*UGT1A1*	For patients who carry 2 decreased function *UGT1A1* alleles, increased risk of jaundice and subsequent nonadherence Consider alternative agents
Atomoxetine	*CYP2D6*	Slower dose titration in intermediate and poor metabolizers. In addition, obtain plasma concentrations 2–4 hr after dosing instead of 1–2 hr
Capecitabine/5-fluorouracil/tegafur	*DPYD*	Increased risk of serious or fatal toxicity in patients with reduced or absent dihydropyrimidine dehydrogenase activity
Carbamazepine/oxcarbazepine	*HLA-B*	Avoid using because of increased incidence of severe cutaneous adverse reactions in patients with the *HLA-B*15:02* allele
Clopidogrel	*CYP2C19*	Normal dosing for ultrarapid metabolizer; alternative antiplatelet therapy in intermediate or poor metabolizers
Codeine	*CYP2D6*	Avoid using codeine because of potential toxicity or lack of efficacy in ultrarapid and poor metabolizers Specific dosing recommendations for extensive and intermediate metabolizers
Efavirenz	*CYP2B6*	In intermediate and poor metabolizers, consider initiating lower doses of efavirenz (200–400 mg/day)
Irinotecan	*UGT1A1*	Reduce the starting dose of irinotecan for *UGT1A1*28* homozygous patients receiving more than 250 mg/m^2
Ivacaftor	*CFTR*	Recommended only for patients with cystic fibrosis who are either homozygous or heterozygous for the *G551D-CFTR* variant

Table 8. CPIC Clinical Recommendations for Drug-Gene Pairs *(Cont'd)*

Drug	Gene	Recommendation
NSAIDs (celecoxib, ibuprofen, meloxicam)	*CYP2C9*	In intermediate metabolizers, start with lowest recommended starting dose (celecoxib/ibuprofen) or 50% of lowest recommended starting dose (meloxicam) and titrate to clinical effect. In poor metabolizers, start with 25%–50% of the lowest recommended starting dose and titrate to clinical effect or 25%–50% of the maximum recommended dose (celecoxib/ibuprofen). Do not use meloxicam in poor metabolizers
Ondansetron	*CYP2D6*	Select an alternative drug that is not predominantly metabolized by CYP2D6 (i.e., granisetron) in CYP2D6 ultra-rapid metabolizers
Phenytoin	*HLA-B*	Reduce initial dosage by 25% in CYP2C9 intermediate metabolizers and by 50% in poor metabolizers Severe cutaneous adverse reactions associated with carriers of the *HLA-B*58:01* allele Use an alternative anticonvulsant
Rasburicase	*G6PD*	Contraindicated in those with G6PD deficiency
Simvastatin	*SLCO1B1*	Dosing recommendations based on genotype at rs4149056 in *SLCO1B1,* including starting at lower dosages or using alternative statins
Siponimod	*CYP2C9*	Maximum 1 mg dose in poor/intermediate metabolizers (**1/*3, *2/*3*) and 2 mg in normal/intermediate metabolizers (**1/*1, *1/*2, *2/*2*)
SSRIs Citalopram: 2C19 Escitalopram: 2C19 Sertraline: 2C19 Fluvoxamine: 2D6 Paroxetine: 2D6	*CYP2D6, CYP2C19*	Alternative drug not predominantly metabolized by CYP2C19 for CYP2C19 ultrarapid metabolizers, and for CYP2C19 poor metabolizers, consider a 50% reduction of recommended starting dosage For CYP2D6 poor metabolizers, consider a 25%–50% reduction of recommended starting dosage
Tacrolimus	*CYP3A5*	Increase starting dosage by 1.5 to 2 times in CYP3A5 intermediate or extensive metabolizers (not to exceed 0.3 mg/kg/day)
Tamoxifen	*CYP2D6*	Use alternative hormonal therapy for CYP2D6 poor metabolizers (also consider alternative for CYP2D6 intermediate metabolizers)
Thiopurines (azathioprine, 6-mercaptopurine, thioguanine)	*TMPT NUDT15*	Dosing recommendations for each drug based on *TMPT* and *NUDT15* genotypes (normal/high, intermediate, and low activity)
Tricyclic antidepressants	*CYP2D6, CYP2C19*	Dosing recommendations for depression based on metabolizer status (ultrarapid, extensive, intermediate, poor) Limited recommendations when using for peripheral neuropathy
Voriconazole	*CYP2C19*	Select an alternative agent that is not dependent on CYP2C19 metabolism, such as isavuconazole, liposomal amphotericin B, or posaconazole, in ultra-rapid and rapid CYP2C19 metabolizers Select an alternative agent that is not dependent on CYP2C19 metabolism in poor CYP2C19 metabolizers, or initiate at a lower-than-normal dose and perform careful therapeutic drug monitoring
Warfarin	*VKORC1/ CYP2C9*	Use available table or algorithms to initiate warfarin dosing based on *VKORC1* and *CYP2C9* genotypes

V. NONLINEAR PHARMACOKINETICS

Patient Case

6. C.M. is a 55-year-old man who is initiated on phenytoin after a craniotomy. His current steady-state phenytoin concentration is 6 mg/L at a dosage of 200 mg/day by mouth. If his affinity constant (Km) is calculated to be 5 mg/L, which is most likely to occur if the dosage is doubled (to 400 mg/day by mouth)?
   A. His concentration will double because phenytoin clearance is linear above the Km.
   B. His concentration will more than double because phenytoin clearance is nonlinear above the Km.
   C. His concentration will stay the same because phenytoin is an autoinducer, and clearance increases with time.
   D. His concentration will increase by only 50% because phenytoin absorption decreases significantly with dosages greater than 300 mg.

A. Michaelis-Menten Pharmacokinetics

$$\text{velocity} = \frac{V_{max} * S}{K_m + S}$$

V_{max} = capacity constant (amount/time)
K_m = affinity constant (amount/volume)
S = substrate concentration (amount/volume)

B. Nonlinear Elimination
   1. Saturation or partial saturation of the elimination pathway

$$\text{rate of elimination (dose)} = \frac{V_{max} * C}{K_m + C}$$

V_{max} = maximum rate of elimination (amount/time)
K_m = concentration where elimination is ½ V_{max} (affinity constant)
C = drug concentration

   2. Note: Nonlinearity occurs when concentration is at or above K_m.
      Example: Phenytoin
      a. V_{max} normal = 7 mg/kg/day
      b. K_m normal = 5.6 mg/L
      c. 50% variability between individuals

VI. NONCOMPARTMENTAL PHARMACOKINETICS

A. Why Noncompartmental Pharmacokinetics?
   1. Identification of the "correct" model is often impossible.
   2. A compartmental view of the body is unrealistic.
   3. Linear regression is unnecessary; it is easier to automate analysis.
   4. Requires fewer and less stringent assumptions
   5. More general methods and equations
   6. There is no need to match all data sets to the same compartmental model.

B. Definitions

1. Zero moment concentration versus time curve
   - Area under the curve (AUC)

$$AUC = \sum \frac{(C_{n+1} + C_n)}{2} * (t_{n+1} - t_n)... + \frac{C_{last}}{k}$$

2. First moment concentration * time versus time curve
   - Area under the first moment curve (AUMC)

$$AUMC = \sum \frac{(C_{n+1} * t_{n+1} + C_n * t_n)}{2} * (t_{n+1} - t_n)... + \frac{C_{last} * t_{last}}{k} + \frac{C_{last}}{k^2}$$

3. Mean residence time (MRT)

$$MRT = \frac{AUMC}{AUC}$$

4. Mean absorption time (MAT)

$$MAT = MRT_{ev} - MRT_{iv}$$

C. Pharmacokinetic Parameter Estimation

1. Clearance

$$Clearance = \frac{dose}{AUC}$$

2. Vd at steady state

$$V_{ss} = \frac{dose * AUMC}{AUC^2}$$

3. Elimination rate constant

$$k = \frac{1}{MRT}$$

4. Absorption rate constant

$$k_a = \frac{1}{MAT}$$

5. Bioavailability

$$F = \frac{D_{iv} * AUC_{ev}}{D_{ev} * AUC_{iv}}$$

VII. DATA COLLECTION AND ANALYSIS

A. Timing of Collection

1. Ensure completion of absorption and distribution phases (especially digoxin [8–12 hours] and aminoglycosides [30 minutes after infusion]).
2. Ensure completion of redistribution after dialysis (especially aminoglycosides [3–4 hours after hemodialysis]).

B. Specimen Requirements

1. Whole blood: Use anticoagulated tube. Examples: cyclosporine, amiodarone
2. Plasma: Use anticoagulated tube and centrifuge; clotting proteins and some blood cells are maintained.
3. Serum: Use red top tube, allow to clot, and centrifuge. Examples: most analyzed drugs including aminoglycosides, vancomycin, phenytoin, and digoxin

Patient Case

7. A drug assay is touted as having high specificity but low sensitivity. Which statement best describes what this means?
   A. The assay cannot distinguish the drug from like products but cannot detect extremely low concentrations.
   B. The assay cannot distinguish the drug from like products and cannot detect extremely low concentrations.
   C. The assay can distinguish the drug from like products and can detect extremely low concentrations.
   D. The assay can distinguish the drug from like products but cannot detect extremely low concentrations.

C. Assay Terminology
   1. Precision (reproducibility): Closeness of agreement between the results of repeated analyses performed on the same sample
      a. Standard deviation (SD): Average difference of the individual values from the mean
      b. Coefficient of variation (CV): SD as a percentage of the mean (relative rather than absolute variation)

$$\text{CV} = \frac{\text{SD}}{\text{Mean}}$$

   2. Accuracy: Closeness with which a measurement reflects the true value of an object
      • Correlation coefficient: Strength of the relationship between two variables
   3. Predictive performance (measure of accuracy): Precision, expressed as the root mean squared error (RMSE)

$$\text{MSE} = \frac{1}{N}\sum_{i=1}^{N} pe_i^2 \qquad \text{RMSE} = \sqrt{mse}$$

      Bias: a.k.a. mean prediction error (ME)

$$\text{ME} = \frac{1}{N}\sum_{i=1}^{N} pe_i$$

      • Prediction error (*pe*) is the prediction minus the true value.

   4. Sensitivity: Ability of an assay to quantitate low drug concentrations accurately; usually the lowest concentration an assay can differentiate from zero
   5. Specificity (cross-reactivity): Ability of an assay to differentiate the drug in question from like substances

D. Assay Methods
   1. Immunoassays
      a. Radioimmunoassay
         i. Advantages: Extremely sensitive (picogram range)
         ii. Disadvantages: Radioimmunoassay kits have limited shelf life because of the short half-life of labels, radioactive waste, and cross-reactivity.
            • Clinical use for assaying digoxin and cyclosporine
      b. Enzyme immunoassay, e.g., enzyme multiplied immunoassay technique
         i. Advantages: Simple, automated, highly sensitive, inexpensive and stable reagents, inexpensive and widely available equipment, no radiation hazards
         ii. Disadvantages: Measuring enzyme activity more complex than radioisotopes, enzyme activity may be affected by plasma constituents, less sensitive than radioimmunoassays

c. Fluorescence immunoassay: TDx (e.g., fluorescence polarization immunoassay): Most common therapeutic drug monitoring assay
   i. Advantages: Simple, automated, highly sensitive, inexpensive and stable reagents, inexpensive and widely available equipment, no radiation hazards
   ii. Disadvantages: Background interference attributable to endogenous serum fluorescence

2. Assays used primarily in pharmacokinetic research studies
   a. High-pressure liquid chromatography
   b. Gas chromatography–mass spectrometry and liquid chromatography–mass spectrometry
   c. Flame photometry
   d. Bioassay

E. Population Pharmacokinetics in Therapeutic Drug Monitoring
1. Population pharmacokinetics useful when
   a. Drug concentrations are obtained during complicated dosing regimens.
   b. Drug concentrations are obtained before steady state.
   c. Only a few drug concentrations are feasibly obtained (limited sampling strategy).
2. Bayesian pharmacokinetics
   a. Prior population information is combined with patient-specific data to predict the most probable individual parameters.
   b. When patient-specific data are limited, there is greater influence from population parameters; when patient-specific data are extensive, there is less influence.
   c. With a small amount of individual data, Bayesian forecasting generally yields more precise results.

Patient Cases

8. K.M., an 80-year-old white woman (52 kg, 64 inches), is admitted to the hospital for pyelonephritis with sepsis. She has a history of myocardial infarction × 2, congestive heart failure, hypertension, osteoporosis, rheumatoid arthritis, and cerebrovascular accident. On admission, her BUN is 25 mg/dL, SCr is 0.92 mg/dL, and Alb is 2.9 g/dL. K.M. is initiated on the following drugs: trimethoprim/sulfamethoxazole (240 mg of the trimethoprim component) intravenously every 12 hours, lisinopril 10 mg daily by mouth, digoxin 0.125 mg daily by mouth, furosemide 40 mg daily by mouth, cimetidine 400 mg twice daily by mouth, acetaminophen 650 mg every 6 hours by mouth, calcium carbonate 500 mg three times daily by mouth, and carvedilol 6.25 mg twice daily by mouth. Which is the best assessment of K.M.'s renal function?
   A. Her SCr is in the normal range, and no dosage adjustments are necessary.
   B. Because of her age, K.M. will have some degree of renal dysfunction, and dosages may need to be adjusted.
   C. Because of the pyelonephritis, K.M. will have renal dysfunction, and dosages may need to be adjusted.
   D. Her SCr is in the normal range but her BUN is elevated, so dosages may need to be adjusted.

9. Which of K.M.'s drug combinations is most likely to alter her SCr concentrations?
   A. Lisinopril and digoxin.
   B. Trimethoprim/sulfamethoxazole and cimetidine.
   C. Furosemide and calcium carbonate.
   D. Acetaminophen and carvedilol.

VIII. PHARMACOKINETICS IN RENAL DISEASE

A. Estimation of Kidney Function Through Glomerular Filtration Rate (GFR) and Creatinine Clearance (CrCl)
   1. Creatinine production and elimination
      a. Creatine is produced in the liver.
      b. Creatinine is the product of creatine metabolism in skeletal muscle, formed at a constant rate for any one person.
      c. Creatinine is filtered at the glomerulus, where it undergoes limited secretion.
      d. CrCl is useful in approximating GFR because:
         i. At normal concentrations of creatinine, secretion is low.
         ii. The creatinine assay picks up a noncreatinine chromogen in the blood but not in the urine.
   2. CrCl calculation to estimate GFR
      • CrCl is calculated from a 24-hour urine collection and the following equation:

$$\text{CrCl (mL/minute/1.73 m}^2\text{)} = \frac{\text{volume of urine/1440 minutes} \times \text{urine creatinine concentration}}{\text{serum creatinine concentration}}$$

      • Normal CrCl
        Healthy young men = 125 mL/minute/1.73 m^2
        Healthy young women = 115 mL/minute/1.73 m^2
      • After age 30, 1% of GFR is lost per year.
   3. CrCl estimation to estimate GFR
      a. Factors affecting SCr concentrations
         i. Sex
         ii. Age
         iii. Weight and muscle mass
         iv. Renal function. Caveats: CrCl estimations worsen as renal function worsens (usually an overestimation).
      b. Jeliffe

$$\text{CrCl (mL/minute/1.73 m}^2\text{)} = \frac{98 - 0.8\,(\text{age} - 20)}{\text{SCr}}$$

      Women: Use 90% of the above equation.

      • Limitations
        SCr concentration must be stable.
        Adults 20–80 years of age (equation only applies to this age group)
        Controversy: Rounding up SCr in patients with low concentrations (less than 0.7–1 mg/dL)

      c. Cockcroft-Gault

$$\text{CrCl(mL/min)} = \frac{(140 - \text{Age}) * (\text{weight})}{72 * \text{Scr}}$$

      Women: Use 85% of the above equation.

      • For "weight": Use actual body weight (ABW) in patients with body mass index (BMI) less than 18.5 kg/m^2, ideal body weight (IBW) in patients with BMI 18.5–25 kg/m^2, and IBW plus 40% of (ABW – IBW) in patients with BMI greater than 25 kg/m^2.

        IBW (men) = 50 kg + 2.3 kg for each inch over 5 feet
        IBW (women) = 45.5 kg + 2.3 kg for each inch over 5 feet

- Generally recommended when making drug dosage adjustments in patients with renal dysfunction, because package insert recommendations generally use this formula to estimate creatinine clearance, and the use of the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equations to make dosing adjustments has not been validated.

- Limitations
  SCr concentration must be stable.
  Developed for adults only
  Not corrected for creatinine standardization (results in lower estimations)
  Not developed in patients with obesity (see weight recommendations above)

d. Salazar-Corcoran

$$\text{CrCl male (mL/min/1.73 m}^2\text{)} = \frac{(137 - \text{age}) * [(0.285 * \text{weight}) + (12.1 * \text{height}^2)]}{51 * \text{SCr}}$$

$$\text{CrCl female (mL/min/1.73 m}^2\text{)} = \frac{(146 - \text{age}) * [(0.287 * \text{weight}) + (9.74 * \text{height}^2)]}{60 * \text{SCr}}$$

- For "weight": Use actual body weight in kg
- For "height": Use meters
- Used for patients with obesity. No better than using Cockcroft-Gault with appropriate weight adjustments (see above)

e. MDRD study equation

Full equation

$$\text{GFR (mL/minute/1.73 m}^2\text{)} = 161.5 * (\text{Scr})^{-0.999} * (\text{age in years})^{-0.176} * 1.180 \text{ (if patient is African American)} * 0.762 \text{ (if patient is a woman)} * (\text{BUN})^{-0.170} * (\text{Alb})^{0.318}$$

Simplified four-variable equation

$$\text{GFR (mL/minute/1.73 m}^2\text{)} = 161.5 * (\text{Scr})^{-1.154} * (\text{age in years})^{-0.203} * 1.212 \text{ (if patient is African American)} * 0.742 \text{ (if patient is a woman)}$$

i. These equations directly estimate GFR (*not* CrCl) and were developed using standardized creatinine concentrations to stage kidney function.
ii. These equations are recommended by the American Kidney Foundation and the European Renal Association to estimate renal function.
iii. Not as accurate when GFR is greater than 60 mL/minute/1.73 m^2
iv. If used for drug dosing, convert value from milliliters per minute per 1.73 m^2 to milliliters per minute.
v. If used for drug dosing and significantly different from Cockcroft-Gault, use clinical judgment and optimize risk versus benefit.

f. CKD-Epi equation (Table 9)
i. These equations directly estimate GFR (not CrCl).
ii. These equations are more accurate than MDRD at higher GFRs (i.e., greater than 60 mL/minute/1.73 m^2). CKD-Epi is recommended by KDIGO as the preferred equation for chronic kidney disease staging.

Table 9. Chronic Kidney Disease Epidemiology Collaboration Equation

Race and Sex	Serum Creatinine (mg/dL)	Equation
African American		
Female	< 0.7	$166 * (Scr/0.7)^{-0.329} * (0.993)^{Age}$
	> 0.7	$166 * (Scr/0.7)^{-1.209} * (0.993)^{Age}$
Male	< 0.9	$163 * (Scr/0.9)^{-0.411} * (0.993)^{Age}$
	> 0.9	$163 * (Scr/0.9)^{-0.411} * (0.993)^{Age}$
White or other		
Female	<0.7	$GFR = 144 * (Scr/0.7)^{-0.329} * (0.993)^{Age}$
	> 0.7	$GFR = 144 * (Scr/0.7)^{-1.209} * (0.993)^{Age}$
Male	< 0.9	$GFR = 141 * (Scr/0.9)^{-0.411} * (0.993)^{Age}$
	> 0.9	$GFR = 141 * (Scr/0.9)^{-1.209} * (0.993)^{Age}$

GFR = glomerular filtration rate; SCr = serum creatinine.

g. Pediatric formulas (Table 10). Do not round up low SCr values in pediatric patients.

Schwartz:

$$GFR\ (mL/minute/1.73\ m^2) = \frac{K * ht\ (cm)}{SCr}$$

Table 10. Schwartz Equation Constants

Age	*K*
Low birth weight ≤ 1 year	0.33
Full term ≤ 1 year	0.45
1–13 years	0.55
13- to 18-year-old adolescent female	0.55
13- to 18-year-old adolescent male	0.7

Note: *K* = 0.413 for 1–13 years old and 13- to 18-year-old adolescent females when using standardized creatinine concentrations (other *K* values have not been updated); this is known as the bedside Chronic Kidney Disease in Children (CKiD) equation.

Counahan-Barratt:

$$GFR\ (mL/minute/1.73\ m^2) = \frac{0.43 * ht\ (cm)}{SCr}$$

4. Factors influencing CrCl estimates
   a. Patient characteristics
      i. Age (↓ production of creatinine with age)
      ii. Female sex (↓ production of creatinine)
      iii. Race (↑ production of creatinine in African Americans)
   b. Disease states and clinical conditions
      i. Spinal cord injuries (↓ muscle mass; ↓ creatinine)
      ii. Amputations (↓ muscle mass; ↓ creatinine)
      iii. Cushing syndrome (↓ muscle mass; ↓ creatinine)
      iv. Muscular dystrophy (↓ muscle mass; ↓ creatinine)
      v. Guillain-Barré syndrome (↓ muscle mass; ↓ creatinine)
      vi. Rheumatoid arthritis (↓ muscle mass; ↓ creatinine)
      vii. Liver disease (↓ creatine; ↓ creatinine)
      viii. Glomerulopathic disease (greater amount of creatinine secretion in relation to filtration)
      ix. Hydration status (dehydration vs. fluid overload)

c. Diet
   i. High-meat protein diets (↑ creatinine ingestion)
   ii. Vegetarians (↓ creatinine ingestion)
   iii. Protein calorie malnutrition (↓ creatinine ingestion)
d. Drugs and endogenous substances
   i. Laboratory interaction: Kinetic alkaline picrate method
      (a) Noncreatinine chromogens: In blood but not in urine
      (b) Cephalosporins (especially cefoxitin): Chromogenic, causing false elevations that are much greater in urine than in blood
      (c) Acetoacetate (elevated in fasting patients, patients with diabetic ketoacidosis): Chromogenic, causing false elevations
   ii. Pharmacokinetic interaction: Drugs compete with creatinine for renal secretion (causing false elevations), cobicistat, trimethoprim, cimetidine, fibric acid derivatives (other than gemfibrozil), and dronedarone.

B. Drug Dosing in Renal Disease
1. Loading dose
   a. In general, no alteration is necessary, but it should be given to hasten the achievement of therapeutic drug concentrations.
   b. Alterations in loading dose must occur if the Vd is altered secondary to renal dysfunction. Example: Decrease digoxin loading doses in renal disease because of a decreased Vd.
2. Maintenance dosage: Alterations should be made in either the dosage or the dosing interval.
   a. Changing the dosing interval
      i. Use when the goal is to achieve similar steady-state concentrations.
      ii. Less costly
      iii. Ideal for limited-dosage forms (i.e., oral medications)
   b. Changing the dosage
      i. Use when the goal is to maintain a steady therapeutic concentration.
      ii. More costly
   c. Changing the dosage and the dosing interval
      i. Often necessary for substantial dosage adjustment with limited-dosage forms
      ii. Often necessary for narrow therapeutic index drugs with target concentrations
         (a) If a drug is given more than once daily, then adjust the interval.
         (b) If a drug is given once daily or less often, then adjust the dosage.

Patient Case

10. S.J. is a 55-year-old man with hepatic dysfunction and an anaerobic infection caused by Prevotella spp. He has a small amount of ascites but is not encephalopathic. He is initiated on metronidazole, and the package insert states that dosages should be decreased by 50% in patients with a Child-Pugh score greater than 9. If he has the following hepatic laboratory values, which best estimates his Child-Pugh score?

    Aspartate transaminase = 85 U/L, alanine transaminase = 56 U/L, alkaline phosphatase = 190 U/L, total bilirubin = 1.8 mg/dL, Alb = 2.9 g/dL, lactic dehydrogenase = 270 U/L, prothrombin time/international normalized ratio = 14.6/1.7, γ-glutamyl transferase = 60 U/L

    A. 3.

    B. 5.

    C. 8.

    D. 11.

IX. PHARMACOKINETICS IN HEPATIC DISEASE

A. Dosage Adjustment in Hepatic Disease
   1. Clinical response is the most important factor in adjusting dosages in hepatic disease.
   2. Low–hepatic extraction ratio drugs
      a. Adjustment of maintenance dosage is necessary only when hepatic disease alters the intrinsic clearance (Cl_{int}).
      b. Alterations in protein binding alone do not require alteration of maintenance dosage, even though total drug concentrations decline.
      c. Loading doses may require reduction.
      d. Examples: carbamazepine, diazepam, phenytoin, warfarin
   3. High–hepatic extraction ratio drugs
      a. Intravenous administration
         i. Usually necessary to decrease maintenance dose rate as hepatic blood flow changes
         ii. Consider effect of hepatic disease on protein binding as it alters free concentrations.
      b. Oral administration: Similar to low–hepatic extraction ratio drugs; necessary to decrease maintenance dose rate when hepatic disease alters Cl_{int}
      c. Examples: haloperidol, morphine, metoprolol, propranolol, verapamil

B. Rules for Dosing in Hepatic Disease
   1. Hepatic elimination of high–extraction ratio drugs is more consistently affected by liver disease than hepatic elimination of low–extraction ratio drugs.
   2. The clearance of drugs that are exclusively conjugated is not substantially altered in liver disease.
   3. Adjustments for some drugs based on Child-Pugh scores (Table 11).

Table 11. Child-Pugh Classification for Liver Disease

	Points		
	1	**2**	**3**
Encephalopathy	0	1 or 2	3 or 4
Ascites	0	+	++
Bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
Prothrombin time (seconds over control) or INR (values in brackets)	0–4 [< 1.7]	4–6 [1.7–2.3]	> 6 [> 2.3]

Pugh score: 5 = normal; 6 or 7 = mild (A); 8 or 9 = moderate (B); >9 = severe (C).

X. PHARMACODYNAMICS

Patient Case

11. Which is the most likely reason that a drug will follow clockwise hysteresis?
    A. Formation of an active metabolite.
    B. Delay in equilibrium between the blood and the site of action.
    C. Tolerance.
    D. Increased sensitivity with time.

A. Definition: Relationship Between Drug Concentrations and the Pharmacologic Response

B. Hill equation

$$E = \frac{E_{max} * C^{y}}{EC_{50}^{y} + C^{y}}$$

E = pharmacologic response
E_{max} = maximum drug effect
EC_{50} = concentration producing half of the maximum drug effect
γ = Hill coefficient that accommodates the shape of the curve

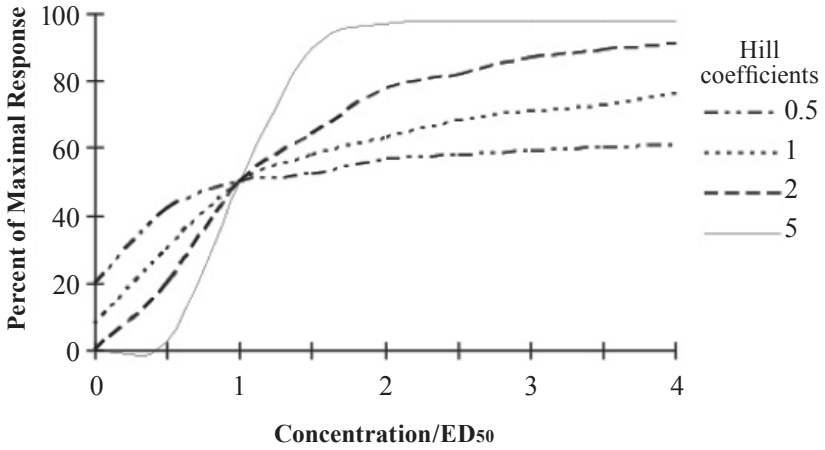

Figure 5. Concentration response plot.

C. Hysteresis Loops. Definition: Concentrations late after a dose produce an effect different from that produced by the same concentration soon after the dose.

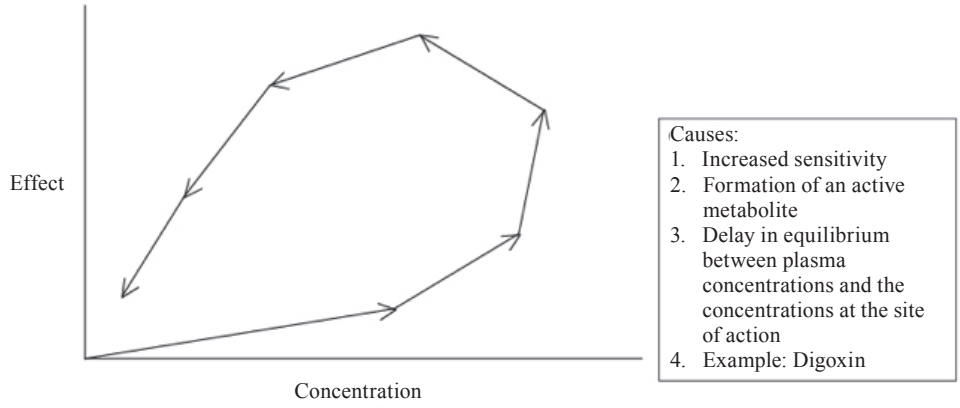
Effect
Concentration
Causes:
1. Increased sensitivity
2. Formation of an active metabolite
3. Delay in equilibrium between plasma concentrations and the concentrations at the site of action
4. Example: Digoxin

Figure 6. Counterclockwise hysteresis.

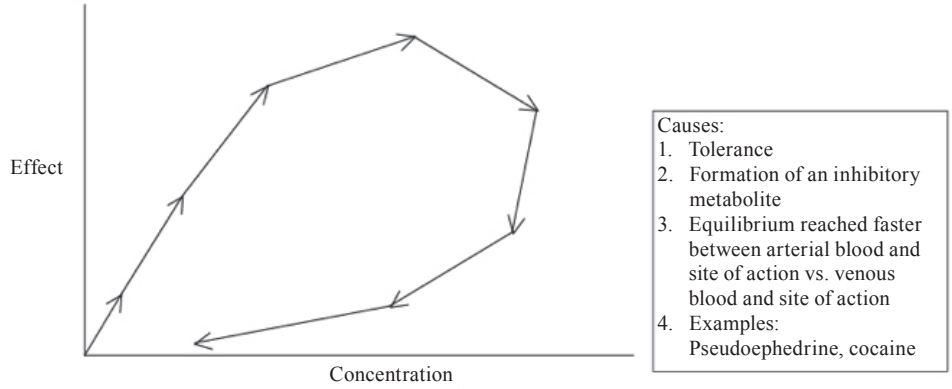
Effect
Concentration
Causes:
1. Tolerance
2. Formation of an inhibitory metabolite
3. Equilibrium reached faster between arterial blood and site of action vs. venous blood and site of action
4. Examples: Pseudoephedrine, cocaine

Figure 7. Clockwise hysteresis.

Patient Cases

12. P.L., a 45-year-old man with end-stage renal disease on dialysis is receiving phenytoin 400 mg/day for a history of tonic-clonic seizures. His phenytoin concentration today is 13.6 mg/L, and his Alb concentration is 4.2 g/dL. Given his current concentrations, which change would best be recommended?
    A. Make no changes to his drug regimen.
    B. Keep the total daily dosage the same, but change the regimen to 200 mg two times/day.
    C. Increase the dosage for better seizure control.
    D. Decrease the dosage to prevent toxicity.

13. N.R. is a 63-year-old man with renal insufficiency who comes to the emergency department in atrial fibrillation with a ventricular rate of 120 beats/minute. Because of his history of ventricular dysfunction, it is decided to initiate him on digoxin for rate control. Which is the best dosing for this patient?
    A. The loading dose should remain the same, but the maintenance dose should be decreased.
    B. The loading dose should be decreased, and the maintenance dose should remain the same.
    C. Neither the loading dose nor the maintenance dose should be adjusted.
    D. Both the loading dose and the maintenance dose should be decreased.

14. P.P. is a 34-year-old man with a history of cerebral palsy and chronic urinary tract infections. He is admitted to the hospital with a *Pseudomonas* urinary tract infection that is resistant to all antibiotics except for aminoglycosides. He is initiated on once-daily tobramycin at 400 mg/day intravenously. Which statement best describes this high-dose, extended-interval aminoglycoside regimen?
    A. It takes advantage of the concentration-dependent killing of aminoglycoside.
    B. It is more efficacious than standard aminoglycoside dosing.
    C. It does not require the monitoring of aminoglycoside concentrations.
    D. It will not cause nephrotoxicity.

XI. THERAPEUTIC DRUG MONITORING (Table 12)

Table 12. Therapeutic Drug Monitoring of Specific Drugs

Drug	Therapeutic Range	Sampling Issues	Comments
Aminoglycosides	Cp = 4–10 mg/L maximum Amikacin = 20–30 mg/L Cp < 2 mg/L minimum Amikacin < 10 mg/L Higher maximum concentrations for high-dose extended-interval dosing	Duration of infusion, timing of first sample after infusion (generally should be ½–1 hour)	High-dose extended-interval ("once-daily") aminoglycoside dosing is generally recommended to decrease toxicity and improve efficacy These regimens are just as effective as traditional dosing, and meta-analyses have demonstrated less nephrotoxicity or no difference
Vancomycin	Bayesian-derived AUC/MIC ratio of 400–600	AUC derived by (1) collecting two concentrations (a near steady-state, post-distributional Cmax at 1–2 hr post-infusion, and a trough) during the same dosing interval and using first-order PK equations to estimate the AUC or (2) collecting one or two concentrations (at least one trough) and using Bayesian software programs to estimate the AUC	Trough-only monitoring of vancomycin is no longer recommended, and clinical PK services should move to AUC/MIC monitoring. If an MIC is not available, assume 1 mg/L. Loading doses are recommended for ICU patients, those receiving renal replacement therapy, and those receiving continuous infusions
Phenytoin	10–20 mg/L Free: 1–2 mg/L	In general, obtain trough concentrations	Percentage free increases with renal failure and hypoalbuminemia Equations to correct: Changes in albumin: $Cp = \frac{Cp'}{(0.9 * \frac{Alb}{4.4}) + 0.1}$ Renal failure: $Cp = \frac{Cp'}{0.5}$ Renal failure with change in albumin: $Cp = \frac{Cp'}{(0.48 * 0.9 * \frac{Alb}{4.4}) + 0.1}$ Induces liver enzymes; susceptible to metabolic drug interactions
Carbamazepine	4–12 mg/L		Autoinduction; active metabolite 10,11 epoxide
Phenobarbital	15–40 mg/L		Enzyme inducer
Valproic acid	50–100 mg/L		Saturable protein binding; percentage free increases with renal failure and hypoalbuminemia
Digoxin	0.8–2.0 mcg/L	Prolonged distribution period necessitates sampling > 6–12 hours after dose	Volume of distribution decreases in renal disease; susceptible to drug interactions
Cyclosporine	100–250 mcg/L	Whole blood samples	Many drug interactions
Lithium	0.3–1.3 mmol/L	Prolonged distribution necessitates sampling 12 hours after dose	
Theophylline	10–20 mg/L		Treat as continuous infusion with sustained-release dosage forms

Cp = concentration of drug in plasma; Vd.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C
In 6 days (2 half-lives), the concentration will decrease from 41.9 mg/L to about 10.5 mg/L; now is the time to redose (Answer C is correct). A 1-g dose given on March 24 will increase the concentration in the blood from 14.1 mg/L to 41.9 mg/L (14.1 + 27.8 mg/L). Given that the half-life is about 3 days, it will take longer than 1 day to reach a concentration of about 10 mg/L (Answer A is incorrect). In 3 days (1 half-life), the concentration will decrease from 41.9 mg/L to about 21 mg/L—still too early to redose (Answer B is incorrect). Redosing can be determined because plenty of information exists about how to calculate when to redose (Answer D is incorrect).

2. Answer: A
F = (100 mg * 25 mg/L/hour)/(200 mg * 50 mg/L/hour) = 25% (Answer A is correct). (Answers B, C, and D are all incorrect).

3. Answer: D
P-glycoprotein is an efflux pump that pumps drugs back into the GI lumen (Answer D is correct). P-glycoprotein is not a plasma protein (Answer A is incorrect), and it does not transfer drugs through the GI mucosa (Answer B is incorrect); rather, it pumps drugs back into the GI lumen. In addition, P-glycoprotein acts in concert with CYP3A4 to diminish oral absorption (Answer C is incorrect).

4. Answer: C
Azithromycin does not inhibit CYP3A4 (Answer C is correct). Erythromycin and clarithromycin are potent inhibitors of CYP3A4 and would be expected to increase cyclosporine concentrations (Answers A and B are incorrect). Cytochrome P450 inhibition is not a drug class effect (Answer D is incorrect).

5. Answer: B
Clopidogrel is a prodrug. Therefore, to be effective, it must be metabolized into the active form. Because this metabolism is primarily performed by CYP2C19 and this patient is a CYP2C19 poor metabolizer, he will not produce as much active drug, increasing the risk of a thrombotic event (Answer B is correct). The clopidogrel metabolite formed does not block the action of aspirin (Answer A is incorrect). Because the clopidogrel metabolite is the active form of the medication, slowing metabolism will not increase bleeding, but instead will have the opposite effect (Answer C is incorrect). Because he is a slow metabolizer of CYP2C19, he will not overproduce the active metabolite (Answer D is incorrect).

6. Answer: B
By definition, clearance becomes nonlinear once the concentration exceeds the K_m (Answer A is incorrect); therefore, the concentrations will more than double (Answer B is correct). Phenytoin is not a significant autoinducer (Answer C is incorrect). Although phenytoin absorption decreases as the dosage is increased, it is not clinically significant until a single dose exceeds 400 mg (Answer D is incorrect).

7. Answer: D
The correct answer is that the assay will be able to distinguish the drug from like products but will not be able to detect extremely low concentrations (Answer D is correct). High specificity means the assay can distinguish the drug from like products (Answers A and B are incorrect), and low sensitivity means the assay cannot detect extremely low concentrations (Answer C is incorrect).

8. Answer: B
Although her SCr is in the normal range, her renal function is decreased because of her age (Answer A is incorrect). After age 30, patients lose around 1 mL/minute/year of CrCl. Therefore, her CrCl needs to be calculated to assess drug dosing (Answer B is correct). Patients with pyelonephritis do not have a decrease in their renal function (Answer C is incorrect). Her elevated BUN is probably a sign of prerenal azotemia caused by dehydration associated with her infection. The BUN measurement is generally not used to assess renal function for drug dosing purposes (Answer D is incorrect).

9. Answer: B

Both trimethoprim/sulfamethoxazole and cimetidine compete with creatinine for secretion in the kidneys, increasing SCr concentrations (Answer B is correct). Although angiotensin-converting enzyme inhibitors may transiently increase SCr concentrations, digoxin does not affect renal function (Answer A is incorrect). Although furosemide may secondarily affect SCr concentrations, calcium carbonate does not affect renal function (Answer C is incorrect). Acetaminophen and carvedilol generally do not affect SCr concentrations (Answer D is incorrect).

10. Answer: C

This patient has 1 point for not being encephalopathic, 2 points for mild ascites, 1 point for the bilirubin concentration, 2 points for the albumin concentration, and 2 points for the INR, for a total of 8 points (Answer C is correct). Normal patients have a Child-Pugh score of 5, which means no hepatic dysfunction (Answers A, B, and D are incorrect).

11. Answer: C

Tolerance leads to a decrease in effect with time; this is clockwise hysteresis (Answer C is correct). The formation of an active metabolite, a delay in equilibrium between the blood and the site of action, and the increased sensitivity with time would lead to an increase in effect with time; this is counterclockwise hysteresis (Answers A, B, and D are all incorrect).

12. Answer: D

The dosage should be decreased to prevent toxicity (Answer D is correct). In renal failure, acidic byproducts build up in the blood and compete with phenytoin for protein binding. Total concentrations must be corrected, and this correction leads to a doubling of the concentration. Therefore, the current concentration is too high, and the dosage should be decreased (Answers A and C are incorrect). Single doses of 400 mg are fine (doses higher than 400 mg should be divided) (Answer B is incorrect).

13. Answer: D

Both the loading dose and the maintenance dose should be decreased (Answer D is correct). In general, loading doses need not be altered in renal dysfunction because they primarily depend on the Vd. However, the digoxin Vd is decreased in renal dysfunction (Answers A and C are incorrect). Because digoxin is eliminated renally, the maintenance dose should be decreased (Answers B and C are incorrect).

14. Answer: A

Aminoglycosides have concentration-dependent killing, and a high-dose, extended-interval aminoglycoside regimen takes advantage of this characteristic (Answer A is correct). However, it has not proved more efficacious than traditional dosing (Answer B is incorrect). Aminoglycoside concentrations still need to be monitored with high-dose, extended-interval therapy (Answer C is incorrect). In addition, high-dose, extended-interval aminoglycoside dosing can still cause nephrotoxicity (although the incidence is generally diminished) (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B
With two concentrations, data are sufficient to calculate an elimination rate constant and, therefore, a half-life (Answers C and D are incorrect; Answer B is correct). In addition, the Vd can be calculated by back extrapolation to the Cmax and use of appropriate equations (because this was the first dose, and therefore it is known that the tobramycin concentration was 0 mg/L before the dose was given) (Answer A is incorrect and Answer B is correct).

2. Answer: A
The elimination rate constant equals (ln 3.6 mg/L − ln 0.9 mg/L)/4 hours = 0.35/hour. The half-life is 0.693/0.35 = 2 hours. The concentration at the end of the infusion equals 3.6 mg/L/e – (0.35 * 1) = 5.1 mg/L. The patient's Vd = dose/change in concentration, or 110 mg/5.1 mg/L = 21.5 L (Answer A is correct; Answers B, C, and D are all incorrect).

3. Answer: B
Her clearance increased because of the improvement in renal function, which increased her elimination rate constant and decreased her half-life (Answer B is correct). The Vd would not be altered by changes in clearance (they are independent) (Answer A is incorrect). With the diuresis and angiotensin-converting enzyme inhibitor, her Vd probably decreased, but clearance would not be altered by changes in Vd (they are independent) (Answer C is incorrect). In addition, if her Vd decreased, her half-life would decrease, not increase (Answer D is incorrect).

4. Answer: C
Because the trough and AUC/MIC are too low, the interval will have to be shortened to increase the concentration (Answers A and B are incorrect). Maintaining the total daily dose will not increase the AUC/MIC to the appropriate range (Answer D is incorrect). Vancomycin largely has linear PK. In the absence of changes to clearance and volume, doubling the dose in a 24-hour period will double the exposure (AUC). Therefore, increasing from 1000 mg daily to 1000 mg every 12 hours will increase the AUC/MIC from 210 to 420 (Answer C is correct).

5. Answer: B
To achieve flucytosine peak concentrations of 50–100 mcg/mL (assuming a trough concentration of 25 mcg/mL, dosing every 6 hours, and 100% bioavailability; flucytosine volume of distribution of 0.7 L/kg; half-life of 3 hours), the concentration must be changed by 25–75 mcg/mL. Using the equation $\Delta Cp = dose/V$, a dosage of 12.5 mg/kg would increase the concentration by only 17.8 mcg/mL. A dosage of 75 mg/kg would increase the concentration by 107 mcg/mL, whereas a dosage of 150 mg/kg would increase the concentration by 214 mcg/mL. The correct dosage is 37.5 mg/kg because it would increase the concentration by 53.6 mcg/mL (Answer B is correct; Answers A, C, and D are all incorrect).

6. Answer: D
Because of the patient's renal failure and low Alb, the total concentration must be corrected. The patient's corrected phenytoin concentration is 14.7 mcg/mL. Therefore, no changes should be made to the dosage (Answer D is correct; Answers A, B, and C are all incorrect).

7. Answer: C
Both of these are immunoassays but they are different (Answer D is incorrect). Because they are both immunoassays, they both use antibodies to bind the molecule of interest (Answer A is incorrect). A brand name for the Abbott fluorescence polarization immunoassay is TDx, which uses a fluorescent label. The term *EMIT* stands for *enzyme multiplied immunoassay technique,* which is an immunoassay that uses an enzyme label (Answer C is correct). Neither of them use radioisotopes (Answer B is incorrect).

8. Answer: D
The digoxin concentration was obtained too close to the 8:00 a.m. dose. The digoxin had not yet had a chance to complete its distribution phase. Once distribution is complete (generally 6–12 hours after the dose), the concentration will be lower and probably within the therapeutic range (Answer D is correct). Therefore, there is no need for the digoxin antibody (Answer A is incorrect), activated charcoal (Answer C is incorrect), or lowering of the dosage (Answer B is incorrect).

9. Answer: C

The correct statistical test is multiple regression. Multiple regression is used to describe the relationship between a dependent variable and two or more independent variables when both the dependent and independent variables are numeric (Answer C is correct). Analysis of variance is used to describe the relationship between a dependent variable and two or more independent variables when the dependent variable is numeric and the independent variables are nominal (Answer A is incorrect). Likewise, analysis of covariance is used to describe the relationship between a dependent variable and two or more independent variables when the dependent variable is numeric and the independent variables are nominal with confounding factors (Answer B is incorrect). Spearman rank correlation is a nonparametric test used to describe the relationship between one dependent and one independent variable when the data are ordinal or numeric and not normally distributed (Answer D is incorrect).

10. Answer: B

Assessing adherence and increasing her dosage is the best recommendation, because the concentration is below the therapeutic range (Answer B is correct). The valproic acid therapeutic range is 50–100 mg/L, and she is well below this concentration. Although some patients are controlled at lower concentrations, this concentration is probably too low (Answer A is incorrect). She definitely does not need a decrease in dosage (Answer C is incorrect). Although total valproic acid concentrations are affected by changes in Alb, her Alb is normal, and obtaining a free concentration is unnecessary (Answer D is incorrect).

11. Answer: B

Codeine's activity is due primarily to its metabolism to morphine by CYP2D6 after administration. Because this patient is a CYP2D6 poor metabolizer, less of the codeine will be metabolized to its active metabolite (Answer B is correct and Answer C is incorrect). Omeprazole does inhibit CYP2C19, but this enzyme does not metabolize codeine (Answer A is incorrect). Metoprolol is a substrate of CYP2D6 but is not an inhibitor or inducer of CYP2C9 Answer D is incorrect).

12. Answer: D

The MDRD and CKD-Epi are actually better estimates of renal function because they directly estimate GFR instead of CrCl (Answer A is incorrect). Although the Cockcroft-Gault equation was developed in hospitalized patients and the MDRD and CKD-Epi equations were developed in ambulatory patients, this does not affect the setting where they can be used (Answer B is incorrect). Moreover, although the equations do have different units (mL/minute vs. mL/minute/1.73 m^2), this can easily be corrected by converting the result of the MDRD or CKD-Epi equation to milliliters per minute (Answer C is incorrect). The best reason for not using MDRD or CKD-Epi for drug dosing is that renal dosing adjustment recommendations published in package inserts are almost always based on CrCl estimates using the Cockcroft-Gault equation (Answer D is correct).

13. Answer: A

Assays with low sensitivity will not be able to detect low drug concentrations, which may still be therapeutic (Answer A is correct). Assays that cannot differentiate between like substances have low specificity (Answers C and D are incorrect). Assays that report highly variable values when repeatedly run on the same sample have low precision (Answer A is correct). Assays that consistently over- or under-measure the true concentration have low accuracy (Answers B and C are incorrect).

Men's and Women's Health

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Men's and Women's Health

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Learning Objectives

1. Recommend appropriate treatment options for patients with menopausal symptoms and osteoporosis.
2. Identify drugs that are considered safe and unsafe during pregnancy and lactation, and differentiate between information resources for pregnancy and lactation.
3. Select the appropriate treatment for infertility or sexual dysfunction on the basis of patient-specific factors.
4. Devise a pharmacotherapeutic plan for appropriate contraceptive use, including assessment of estrogen- and progestin-related adverse effects or drug interactions, contraceptive method mishaps, and use of emergency contraception.
5. Identify common menstrual disorders and sexually transmitted diseases and recommend appropriate pharmacotherapy.

Abbreviations in This Chapter

ACE	Angiotensin-converting enzyme
aPTT	Activated partial thromboplastin time
BMD	Bone mineral density
BUM	Backup method
CHD	Coronary heart disease
COC	Combined oral contraceptive
CYP	Cytochrome P450
CVD	Cardiovascular disease
DMPA	Depot medroxyprogesterone acetate
DVT	Deep venous thrombosis
DXA	Dual-energy x-ray absorptiometry
EC	Emergency contraception
EPT	Estrogen and progestogen therapy
ET	Estrogen only therapy
FRAX	Fracture Risk Assessment Tool
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
GSM	Genitourinary syndrome of menopause
hCG	Human chorionic gonadotropin
HSV	Herpes Simplex Virus
HT	Hormone therapy
IUD	Intrauterine device
IUS	Intrauterine system
LARC	Long-acting reversible contraception
LH	Luteinizing hormone
NSAIDs	Nonsteroidal anti-inflammatory drugs
OC	Oral contraceptive
OTC	Over the counter
PCOS	Polycystic ovary syndrome
PDE	Phosphodiesterase
PID	Pelvic inflammatory disease
POP	Progestin-only pill/minipill
VTE	Venous thromboembolism

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. M.T. is a 72-year-old white man (height 69 inches, weight 68 kg) with a history of hypertension who admits smoking one pack of cigarettes per day and having a poor diet. He states that he walks on his treadmill 30 minutes a day. His bone mineral density (BMD) T-score is –2.1 at the hip and –2.2 at the spine. His fracture history includes a fall at age 68 with an ankle fracture. His Fracture Risk Assessment Tool (FRAX) score (10-year major fracture probability) is 14%, and his probability of hip fracture is 6.7%. Which best describes M.T.'s condition?
   A. He has low bone mass (osteopenia) of the hip and spine.
   B. He has osteoporosis of the spine and low bone mass (osteopenia) of the hip.
   C. He has osteoporosis of the hip and spine.
   D. He has normal BMD of the hip and spine.

2. Which treatment is best for M.T.?
   A. Take calcium 1200 mg orally daily, vitamin D 800 international units orally daily, and alendronate 70 mg orally weekly.
   B. Take calcium 1200 mg orally daily and vitamin D 600 international units orally daily, and begin weight-bearing exercise.
   C. Take calcium 1200 mg orally daily, vitamin D 600 international units orally daily, and raloxifene 60 mg orally daily.
   D. Take calcium 1200 mg orally daily, vitamin D 400 international units orally daily, and risedronate 35 mg orally weekly, and begin weight-bearing exercise.

3. A 29-year-old woman (height 65 inches, weight 63 kg) has a history of two deep venous thromboses (DVTs) but is otherwise healthy; she is seeking to become pregnant. She currently takes warfarin

3 mg orally daily. Which regimen is the best recommendation for this patient?

A. Continue current warfarin dose to prevent clots during pregnancy.

B. Continue warfarin therapy but increase the dose to prevent clots during pregnancy.

C. Discontinue warfarin; start enoxaparin 40 mg subcutaneously daily until pregnant and continue through pregnancy.

D. Discontinue warfarin; start heparin 5000 units subcutaneously every 8 hours daily until 12 weeks pregnant, and then reinitiate warfarin.

4. J.K. is a 51-year-old postmenopausal woman with severe hot flashes that have not resolved with venlafaxine 75 mg orally daily. She is otherwise healthy, with no history of cancer and no surgical procedures. She is given conjugated estrogen 0.625 mg orally daily. Which treatment is best for J.K.?

A. No other drug is needed; estrogen alone is sufficient for hot flashes.

B. No other drug is needed; estrogen should be discontinued, and she should continue on venlafaxine.

C. Venlafaxine should be continued and Medroxyprogesterone acetate should be added to decrease the risk of stroke.

D. Venlafaxine should be discontinued and Medroxyprogesterone acetate should be added to decrease the risk of endometrial cancer.

5. C.S. is a 49-year-old postmenopausal woman experiencing severe hot flashes, vaginal dryness, and pain during sexual intercourse. C.S. has a history of irregular heavy uterine bleeding, which resulted in a total hysterectomy 5 months ago. Her hot flashes are affecting her quality of life. Which treatment is best to recommend for C.S.?

A. Estradiol vaginal cream (Estrace) 0.1 mg/g.

B. Conjugated estrogen and medroxyprogesterone acetate (Prempro) 0.625 mg/2.5 mg tablets.

C. Conjugated estrogen (Premarin) 0.3-mg tablets.

D. Ospemifene (Osphena) 60-mg tablets.

6. S.F. is a 20-year-old woman initiated on ethinyl estradiol 30 mcg/drospirenone 3 mg oral tablets 5 months ago for contraception. She was recently prescribed lamotrigine for bipolar disorder. Which best describes the drug interaction that may occur with ethinyl estradiol/drospirenone and lamotrigine in this patient?

A. The effectiveness of ethinyl estradiol and drospirenone may be decreased.

B. The effectiveness of lamotrigine may be increased.

C. The effectiveness of lamotrigine may be decreased.

D. The effectiveness of ethinyl estradiol and drospirenone may be increased.

7. A study compares the incidence of herpes simplex genital infections in patients receiving suppressive therapy with acyclovir versus valacyclovir. After 1 year of follow-up, 25% in the acyclovir group and 20% in the valacyclovir group experience a recurrent infection ($p<0.05$). Which best represents how many patients (in 1 year) would need to be treated with valacyclovir over acyclovir to prevent one recurrent infection?

A. 5.

B. 20.

C. 25.

D. There is insufficient information to calculate this number.

8. K.M. is a 28-year-old woman (height 68 inches, weight 98 kg) with a history of migraine with aura who is seeking contraception. Her blood pressure today is 135/82 mm Hg; she denies smoking and alcohol use and states that she would like to have children in a year or so. Which is the best contraceptive agent for K.M.?

A. Levonorgestrel intrauterine system (Mirena IUS).

B. Oral tablet norethindrone (Micronor).

C. Transdermal ethinyl estradiol/etonogestrel patch (Xulane).

D. Oral ethinyl estradiol/desogestrel oral tablet (Mircette).

9. L.L. is a 38-year-old woman who has been trying to conceive for the past 7 months. Her husband's medical examination is normal; L.L. is not ovulating every month. She has not tried any medications previously to induce ovulation. Which medication is best to initiate in L.L. to induce ovulation?
   A. Ovidrel (human chorionic gonadotropin [hCG]).
   B. Synarel (nafarelin/gonadotropin-releasing hormone [GnRH] agonist).
   C. Menopur (human menopausal gonadotropin [hMG]).
   D. Clomiphene.

10. T.G. is a 22-year-old woman who comes to a community pharmacy and asks about emergency contraception (EC). She states that she was out of town for the weekend and was swimming when her contraceptive vaginal ring slipped out. She has been without the ring for 3 days because she did not have a new one with her for replacement. She states she had unprotected intercourse 4 nights ago. She is worried about becoming pregnant. Which is the best recommendation for T.G.?
   A. Recommend that she see her physician for a levonorgestrel 1.5 mg prescription.
   B. Recommend EC; it may still be effective because she is within the 120-hour time window.
   C. Do not recommend EC; it may be ineffective because she is beyond the 72-hour time window.
   D. Do not recommend EC; instead, recommend that she insert a new contraceptive vaginal ring.

11. K.S. is a 45-year-old man who has difficulty maintaining an erection during intercourse. His medical history includes diabetes mellitus and hyperlipidemia. His drugs include aspirin, metformin, and pravastatin. Blood pressure is 130/81 mm Hg, hemoglobin A1C 6.2, total cholesterol 195 mg/dL, low-density lipoprotein cholesterol (LDL) 106 mg/dL, high-density lipoprotein cholesterol (HDL) 54 mg/dL, triglycerides 145 mg/dL, total testosterone concentration 970 ng/dL (reference range 270–1070 ng/dL), and free testosterone concentration 22 ng/dL (reference range 9–30 ng/ dL). Which drug is best to initiate for his erectile dysfunction?
   A. Vardenafil.
   B. Testosterone transdermal patch.
   C. Yohimbine.
   D. Fluoxetine.

12. T.M., a 33-year-old man, has a history of intravenous drug abuse and lives in and out of homeless shelters. He is taken to the emergency department by ambulance after experiencing paralysis on the right side of his body. The people at the shelter thought he might be having a stroke. In the emergency department, a laboratory profile was performed, which was positive for the Venereal Disease Research Laboratory test (syphilis test) with 10 white blood cells/mm^3. T.M. has no known significant medical history (except for treatment of a sexually transmitted disease [STD]), but he is allergic to penicillin (anaphylactic reaction). Which therapy is best for T.M.?
   A. Levofloxacin 750 mg intravenously for one dose.
   B. Penicillin G 4 million units every 4 hours intravenously for 14 days after penicillin desensitization.
   C. Benzathine penicillin G 2.4 million units intramuscularly every week for 3 weeks after penicillin desensitization.
   D. Azithromycin 500 mg intravenously or orally daily for 6 weeks.

13. A prospective double-blind study compared the effects of three different antivirals—acyclovir, famciclovir, and valacyclovir—in 360 patients with first-episode genital herpes. Which statistical test is best to compare the mean duration of time until the lesions healed?
   A. Analysis of variance (ANOVA).
   B. Chi-square test.
   C. Mann-Whitney U test.
   D. Student t-test.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain I: Patient-Centered Pharmacotherapy, Tasks 1-a, 1-b, 1-c, 1-d, 1-e, 1-f, 1-g, 1-h, 1-i, 1-j, 1-k, 1-l, 1-m, 1-n, 1-o, 1-p, 1-q, 2-a, 2-b, 2-c, 3-a, 3-b, 3-c, 3-d, 4-a
2. Domain II: Application of Evidence to Practice and Education, Tasks 1-c, 1-d
3. Domain III: Healthcare Systems and Population Health, Tasks 1-b, 1-c, 2-a, 3-b, 3-c

I. HORMONE THERAPY AND MENOPAUSE

A. Background of Menopause
   1. Definition: Cessation of menstrual periods for 1 year, also known as final menstrual period, loss of ovarian follicular function
   2. Average age of menopause is 52 years, but age ranges from 40 to 58 years.
   3. Common symptoms
      a. Vasomotor symptoms, also known as hot flashes
         i. Most common reason for treatment
         ii. May interrupt sleep and cause insomnia
         iii. May affect quality of life
         iv. Occur in 75%–85% of women, usually within 12–24 months after the last menstrual period.
         v. May cause increased skin temperature, nausea, dizziness, headache, palpitations, diaphoresis, and night sweats.
      b. Genitourinary syndrome of menopause (GSM): Encompasses both vaginal and urinary symptoms (Menopause 2014;21:1-6, Menopause 2017;24:1-26)
         i. Decrease in estrogen causes thinning of hair of the mons and shrinkage of the labia minora; vulvovaginal atrophy (VVA) leads to pruritus and pain.
         ii. Loss of lubrication leads to dyspareunia (pain during sexual intercourse).
         iii. Vaginal pH changes and becomes more basic (from 4.5−5 to 6−8), creating a favorable environment for bacterial colonization.
         iv. Thinning of urethra and bladder lining and decreased muscle tone result in recurrent episodes of urinary frequency, urgency with dysuria, and urinary tract infections.

B. Treatments
   1. Individualization of therapy is essential. Need to consider the woman's medical history.
      a. History of cancer, specifically breast cancer
      b. History of cardiovascular disease (CVD), stroke, hypertension
      c. Quality of life with menopausal symptoms
   2. Hormone therapy (HT) is the all-encompassing term that includes estrogen and progestogen therapy (EPT), estrogen-only therapy (ET), progestogen-only therapy (PT), and estrogen-receptor (ER) agonists or antagonists.
      a. FDA-Approved indications for various HT: Treatment of moderate to severe vasomotor symptoms (VMS), treatment of moderate to severe VVA because of menopause, prevention of postmenopausal osteoporosis, hypoestrogenism caused by hypogonadism, castration or premature ovarian failure.
      b. Recommendations for HT
         i. Menopausal symptom relief
            (a) Moderate to severe vasomotor symptoms
               1. Primary indication for HT
               2. Recommend lowest effective dose.
               3. For women younger than 60 or women who are within 10 years of menopause onset without contraindications or at a high risk of CVD or breast cancer, assess the baseline risk of breast cancer and CVD, and consider risk when making recommendation.
            (b) GSM encompasses
               1. Moderate to severe vaginal symptoms – Recommend local ET versus systemic therapy if treating vaginal symptoms only AND
               2. Urinary health – Systemic HT may worsen stress incontinence; local ET therapy may help with overactive bladder

(c) Sexual function – HT not recommended for sole treatment of diminished libido
(d) Osteoporosis – EPT and ET indication for prevention, ↓ osteoporotic fractures, used only when alternative therapies are not appropriate; ER agonists/antagonists (conjugated estrogens 0.45 mg plus bazedoxifene 20 mg oral tablets and raloxifene) may also be used for osteoporosis. See section below.

ii. Risk assessment (J Clin Endocrinol Metab 2015;100:3975-4011)
(a) For women with a high risk of VTE who request HT, the non-oral route HT at lowest effective dose is recommended if not contraindicated.
(b) For women with a high risk or history of breast cancer, a nonhormonal treatment is recommended for symptom relief.
(c) For women with a high risk of CVD (known myocardial infarction [MI], cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, diabetes mellitus, chronic kidney disease, and 10-year CVD risk greater than 10%), a nonhormonal treatment is recommended for symptom relief.
(d) For women with a moderate risk of CVD, transdermal estradiol with appropriate use of progestogen (individualized) is recommended if hormone therapy is needed.

c. Benefits and risks of estrogen and progestogens
i. Benefits of estrogen
(a) Relieves genitourinary atrophy (if only symptom, may use estrogen vaginal product locally)
(b) Relieves vasomotor instability
(c) Osteoporosis: Reduction in hip fractures by 25%; reduction in vertebral fractures by 50%. Estrogen reduces the rate of bone resorption but does not reverse bone loss.
(d) It was once thought to lower LDL and increase HDL; however, it was not shown to lower coronary heart disease (CHD) according to the Heart and Estrogen/Progestin Replacement Study (HERS; JAMA 1998;280:605-13) and the Women's Health Initiative (WHI; JAMA 2002;288:321-33) trials.
(e) May help improve sleep by decreasing hot flashes
(f) May help stabilize mood swings but is not indicated for mood disorders

ii. Risks of estrogen
(a) Adverse effects: Bloating, headache, breast tenderness (5%–10%)
(b) Endometrial cancer: Risk increases with unopposed estrogen use in women with an intact uterus.
(1) Cancer risk depends on duration of estrogen use.
(2) Cancer risk increases 8-fold for 10–20 years of estrogen use.
(3) Not recommended for use in women with a history of endometrial cancer. Women with early stage, low-risk endometrial cancers (grade 1 and 2 endometrioid subtypes with negative estrogen and progesterone receptors) who used HT may have similar recurrence and death rates but overall recommendation is to avoid HT use in women with endometrial cancer, especially advanced stages (Menopause 2017;24:1-26).
(4) A progestogen is recommended in all women with an intact uterus using estrogen (JAMA 1996;275:370-5, Menopause 2017;24:1-26).
(c) Breast cancer with unopposed estrogen: Uncertain
(1) WHI showed no increased risk and a nonsignficant decrease in risk in women who use estrogen for an average of 7.2 years. May increase relative risk among women who take estrogen for longer than 5 years, though some studies have not shown this risk (Menopause 2017;24:1-26).

(2) Not recommended for use in women with a history of breast cancer (Menopause 2017;24:1-26).
(3) Risk seems to increase with the addition of the progestogen and be related to the length of use. The risk is small and decreases after discontinuation of use.

(d) CHD: Possible increased risk of cardiovascular outcomes; not recommended for coronary protection at any age (see text that follows for further information).
(e) Gallbladder effects: Use of oral estrogen may increase risk of gallbladder disease that may result in gallstones, cholecystitis, cholecystectomy. Risk is slightly lower with medroxyprogesterone acetate in combination with estrogen (Menopause 2017;24:1-26).

iii. Benefits of progestogen (progestogen is an umbrella term for progesterone [natural] and progestins [synthetic]):
(a) Decreased risk of estrogen-induced irregular bleeding
(b) Decreased risk of endometrial hyperplasia and carcinoma

iv. Risks of progestogen
(a) Adverse effects: Bloating, weight gain, irritability, depression (dose related)
(b) Unpredictable endometrial bleeding with continuous estrogen/progestin during first 8–12 months (30%–50%)

v. Selected outcomes related to EPT and ET
(a) Cardiovascular outcomes with conjugated estrogens and medroxyprogesterone acetate (JAMA 1998;280:605-13)
(1) A longer duration of use leads to a greater decrease in relative hazards in nonfatal MI and CHD death; however, there was an increased risk of venous thromboembolism (VTE) and gallbladder disease.
(2) Conclusions of study: HT was not appropriate to initiate for secondary prevention of CHD, but for women already using HT, long-term use might result in a decrease in CHD.
(3) A follow-up study suggested that older women with CHD who used HT for longer than 6.8 years had a higher risk of VTE and biliary tract surgery (JAMA 2002;288:58-66).

(b) Other findings related to cardiovascular outcomes from various trials
(1) Venous thromboembolism
(A) Observational studies indicated increased risk.
(B) A randomized controlled trial, the WHI (JAMA 2002;288:321-33), found increased risk in the EPT arm (18 additional VTEs per 10,000 women per year of EPT) and in the estrogen only therapy (ET) arm (7 additional VTEs per 10,000 women per year of ET).
(C) In WHI, when EPT and ET were initiated in women 50–59 years of age, the risk of VTE was lower in this age group (11 additional VTEs per 10,000 women per year of EPT and 4 additional VTEs per 10,000 women per year of ET).
(2) Stroke
(A) Both EPT and ET showed an increased risk of stroke (8 additional strokes per 10,000 women per year of EPT and 11 additional strokes per 10,000 women per year of ET).
(B) Women 50–59 years of age had no significant increase in stroke with EPT in the WHI, but in the ET group alone, risk doubled. Nurses' Health Study showed similar results (Cochrane Database Syst Rev 2015;3:CD002229).
(3) Coronary heart disease
(A) Observational studies indicated therapy may decrease CHD risk, but most women were younger than 55 and had entered menopause within the past 2–3 years.

(B) Randomized controlled trials indicated an increased risk of CHD, but women had an average age of 63–64 years and had entered menopause about 10 years earlier. When adjusted for age, the estrogen-only arm of the WHI trial matches observational data, indicating a lower risk of CHD in younger patients.

(C) Data show women who begin HT within 10 years of entering menopause may have a lower risk of CHD, whereas older women may have a higher risk of CHD.

(4) Coronary artery calcium, a marker associated with atheromatous plaque burden and CHD risk, has been decreased in some observational studies. In the WHI study, estrogen-only arm participants had lower concentrations of coronary artery calcium after 7 years of treatment.

(5) Subclinical atherosclerosis, measured as carotid intima-media thickness, is reduced in women who started estrogen therapy with or without a progestogen less than 6 years past the time of menopause compared with placebo. This was not true in women who started hormone therapy 10 years or more after menopause onset (N Engl J Med 2016;374:1221-31).

(6) WHI findings (JAMA 2002;288:321-33). The WHI trial included conjugated estrogens and medroxyprogesterone acetate in healthy women 50–79 years of age for primary prevention of CHD. Controversy exists because the average age of women was older; thus, increases in breast cancer or CVD could be caused by age (Table 1).

Table 1. Summary of WHI Outcomes for EPT Use

Risk or Benefit	Relative Risk	Absolute Risk Each Year
Blood clots	2.11, or 111% ↑	18 more cases in 10,000 women
Dementia[a]	2.05, or 105% ↑	23 more cases in 10,000 women > 65
Strokes	1.41, or 41% ↑	8 more cases in 10,000 women
Heart attacks	1.29, or 29% ↑	7 more cases in 10,000 women
Breast cancer	1.26, or 26% ↑	8 more cases in 10,000 women
Hip fractures	0.66, or 33% ↓	5 fewer cases in 10,000 women
Colon cancer	0.63, or 37% ↓	6 fewer cases in 10,000 women

[a]Women's Health Initiative Memory Study.

EPT = estrogen and progestogen therapy; WHI = Women's Health Initiative

(c) Further information suggests increased risk of ovarian cancer (data conflicting); long-term use greater than 5 years may increase risk, particularly in estrogen-only therapy; overall risk of occurrence considered rare, according to WHI data (JAMA 2009;302:298-305). A recent meta-analysis showed that hormone therapy, regardless of type or regimen, was associated with an increased risk of ovarian cancer (Menopause 2016;4:417-24, Menopause 2017;24:1-26).

(d) Lung cancer may be increased in older women with a history of smoking (Lancet 2009;374:1243-51); some data are conflicting. Seems to be more associated with EPT use than with ET use.

(e) Cumulative 18-year follow-up on WHI trials of conjugated equine estrogens (0.625 mg/day) and medroxyprogesterone acetate (2.5mg/day) used for a median of 5.6 years or conjugated equine estrogens alone for a median of 7.2 years showed no difference in all-cause and cause-specific mortality risk (JAMA 2017;318(10):927-938).

vi. Formulations
  (a) Oral: Used for vasomotor symptoms, also covers GSM if concomitant.
  (b) Transdermal: For women who are intolerant of oral preparations, used for vasomotor symptoms, also covers GSM if concomitant, according to 2015 Endocrine Society clinical practice guideline first-line formulation for women with moderate risk of CVD if estrogen is needed.
  (c) Vaginal and local preparations: For women with GSM. In general, topical treatment is sufficient and should be tried before oral preparations for patients experiencing no other symptoms (Femring vaginal ring is only vaginal preparation indicated for vasomotor symptoms).

vii. Hormone regimens
  (a) Therapy duration: Lowest dose for least amount of time. Check after 3 months to 1 year, and try to discontinue if asymptomatic; if symptoms recur, treat for an additional 3 months; best to limit treatment to less than 5 years
  (b) Unopposed estrogen
    (1) Women with a uterus must have a progestogen and cannot use estrogen alone; use of estrogen alone in women with a uterus increases the risk of endometrial cancer. Original reference: JAMA 1996;275:370-5.
    (2) Estrogen taken daily without interruption is suggested for women with a hysterectomy.
    (3) Transdermal estradiol patches in women who are intolerant of oral preparations or want nondaily administration
  (c) Estrogen plus cyclic progestogen
    (1) Continuous estrogen daily
    (2) Cyclic progestogen such as medroxyprogesterone acetate 5−10 mg/day or the equivalent for 10–14 days/month
    (3) Similar to female cycle, with a withdrawal bleed each cycle
  (d) Estrogen plus continuous progestogen
    (1) Continuous estrogen daily
    (2) Continuous progestogen such as medroxyprogesterone acetate 1.5–2.5 mg/day or the equivalent without interruption
    (3) Irregular menstrual cycle for the first 8–12 months of therapy, leading to amenorrhea
  (e) Intermittent
    (1) Continuous estrogen daily
    (2) Three days on progestogen, 3 days off
    (3) Seldom used

viii. Monitoring criteria
  (a) Monthly: Breast self-examination
  (b) Annually: Breast examination by provider, mammography (or biannually per U.S. Preventive Services Task Force), pelvic examination
  (c) Evaluation of vaginal bleeding
    (1) Unopposed estrogen: Any episode of vaginal bleeding unless the woman has had a health assessment deemed normal in the past 6 months
    (2) Estrogen plus cyclic progestogen: If bleeding occurs other than at the time of expected withdrawal bleeding
    (3) Estrogen plus continuous progestogen: If bleeding is heavier than normal, is prolonged (longer than 10 days at a time), is frequent (more often than monthly), or persists for more than 10 months after beginning therapy

ix. Products and dosing (Tables 2, 3, 4, 5, and 6)

Table 2. Oral Estrogen Products

Brand Name	Generic Name	Strengths (mg)
Estrace	17β-Estradiol	0.5, 1, 2
Femtrace	Estradiol acetate	0.45, 0.9, 1.8
Menest	Esterified estrogens	0.3, 0.625, 1.25, 2.5
Various generics	Estropipate	0.75, 1.5, 3, 6
Premarin	Conjugated estrogens	0.3, 0.45, 0.625, 0.9, 1.25
Cenestin	Conjugated estrogens	0.3, 0.45, 0.625, 0.9, 1.25
Enjuvia	Conjugated estrogens	0.3, 0.45, 0.625, 0.9, 1.25

Table 3. Vaginal Estrogen Products

Formulation	Brand Name	Generic Name and Strength	Dose
Vaginal creams	Estrace	Micronized estradiol (0.1 mg/g)	Initial: 2–4 g/day for 1–2 wk; then gradually reduced to half the initial dose for 1–2 wk, followed by maintenance of 1 g/day applied vaginally one to three times weekly
	Premarin	Conjugated estrogens (0.625 mg/g)	Atrophic vaginitis: Use 0.5–2 g/day applied vaginally for 21 days and then 7 days off; may also use twice-weekly regimen of 0.5 g intravaginally for dyspareunia
Vaginal rings	Estring	17β-Estradiol (2-mg ring that delivers 7.5 mcg/day)	1 ring every 3 mo inserted vaginally
	Femring	Estradiol acetate (0.05 or 0.1 mg/day)	
Vaginal tablet	Vagifem, Yuvafem	Estradiol hemihydrate (10 or 25 mcg/day)	1 vaginal tablet once daily for 2 wk; then 1 tablet twice weekly
	Imvexxy	Estradiol inserts (4 or 10 mcg)	1 vaginal insert daily for 2 wk; then 1 vaginal insert twice weekly

Table 4. Transdermal Estrogen Products

Brand Name	Formulation	Estrogen Provided (mg/day)	Dose	Unique Traits and Counseling Points
Alora	17β-Estradiol matrix patch	0.025, 0.05, 0.075, 0.1	1 patch twice weekly	Rotate sites of application to avoid irritation for all patches Minivelle should be placed on dry skin below umbilicus on abdomen or buttocks Menostar is lowest-dose transdermal patch available; indicated only for prevention of postmenopausal osteoporosis
Climara		0.025, 0.0375, 0.05, 0.06, 0.075, 0.1	1 patch weekly	
Minivelle		0.025, 0.0375, 0.05, 0.075, 0.1	1 patch twice weekly	
Vivelle-Dot, Dotti		0.025, 0.0375, 0.05, 0.075, 0.1	1 patch twice weekly	
Menostar		0.014	1 patch weekly	
Esclim		0.025, 0.0375, 0.05, 0.075, 0.1	1 patch twice weekly	
Estraderm		0.05, 0.1	1 patch twice weekly	
Divigel 0.1%	17β-Estradiol transdermal gel	Unknown	0.25, 0.5, 0.75, or 1 g of gel	Apply Divigel to one leg daily, alternate sites daily
Elestrin 0.06%		0.52 (0.0125 absorbed), 1.04 (0.0375 absorbed)	0.25, 0.5, 0.75, or 1 g of gel	Apply Divigel to one leg daily, alternate sites daily
EstroGel 0.06%		0.75 (0.035 absorbed)	0.25, 0.5, 0.75, or 1 g of gel	Apply Divigel to one leg daily, alternate sites daily
Evamist	17β-Estradiol transdermal spray	1.53 (0.021 absorbed)	Initial 1 spray/day (1.53 mg) increasing to 2 or 3 sprays/day	1 spray on forearm daily, can increase to 2 or 3 sprays on forearm daily

Table 5. Combination Products

Brand Name	Generic Name	Hormone Strengths	Dose
Activella, Amabelz, Mimvey, Lopreeza	17β-Estradiol/ norethindrone acetate	0.5 mg estrogen, 0.1 mg progestogen (Mimvey unavailable at 0.5/0.1 mg strength); 1 mg estrogen, 0.5 mg progestogen	1 tablet daily
Angeliq	17β-Estradiol/ drospirenone	1 mg estrogen, 0.5 mg progestogen; 0.5 mg estrogen, 0.25 mg progestogen	1 tablet daily
Climara Pro	17β-Estradiol/ levonorgestrel	0.045 mg estrogen, 0.015 mg progestogen	1 patch weekly
CombiPatch	17β-Estradiol/ norethindrone acetate	0.05 mg estrogen, 0.14 mg progestogen 0.05 mg estrogen, 0.25 mg progestogen	1 patch twice weekly
Bijuva	17β-Estradiol/ progesterone	1 mg estrogen, 100 mg progestogen	1 capsule every evening with food
Femhrt, Jinteli, Fyavolv	Ethinyl estradiol/ norethindrone acetate	0.0025 mg estrogen, 0.5 mg progestogen (Femhrt, Fyavolv) 0.005 mg estrogen, 1 mg progestogen (Jinteli, Fyavolv) 0.002 mg estrogen, 1 mg progestogen 0.003 mg estrogen, 1 mg progestogen	1 tablet daily

Table 5. Combination Products *(Cont'd)*

Brand Name	Generic Name	Hormone Strengths	Dose
Prefest	17β-Estradiol/ norgestimate	1 mg estrogen, 0.09 mg progestogen	3 days of estrogen tablets only, 3 days of estrogen and progestogen
Premphase	Conjugated estrogens/ medroxyprogesterone acetate	0.625 mg estrogen with 5 mg progestogen	0.625 mg/day for 14 days; then 0.625 mg and 5 mg/day for 14 days
Prempro	Conjugated estrogens/ medroxyprogesterone acetate	0.625 mg estrogen with 2.5 or 5 mg progestogen 0.3 or 0.45 mg estrogen with 1.5 mg progestogen	1 tablet daily

Table 6. Progestogen Products[a]

Brand Name	Generic Name	Dosage Strengths and Formulation
Aygestin	Norethindrone acetate	5-mg oral tablets
Megace	Megestrol acetate	20-, 40-mg oral tablets
Camila, Deblitane, Errin, Heather, Incassia, Jencycla, Lyza, Micronor, Nora-BE, Norlyda, Norlyroc, Sharobel, Tulana	Norethindrone	0.35-mg oral tablets
Mirena	Levonorgestrel	20 mcg/day released from intrauterine system
Skyla	Levonorgestrel	14 mcg/day released from intrauterine system
Liletta	Levonorgestrel	14.3 mcg/day (average) from intrauterine system
Kyleena	Levonorgestrel	17.5 mcg/day released from intrauterine system
Crinone 4%, 8%	Progesterone gel	45-mg vaginal applicator vaginally, 90-mg vaginal applicator vaginally
Endometrin	Progesterone vaginal suppository	100 mg vaginal suppository
Prometrium	Micronized progesterone in peanut oil	100- and 200-mg oral capsules
Provera	Medroxyprogesterone acetate	2.5-, 5-, and 10-mg oral tablets

[a]Not all products approved for menopause therapy.

d. Selective estrogen receptor modulators, also known as estrogen receptor agonist/antagonists, indicated for use in menopause symptoms.
   i. Ospemifene 60-mg oral tablets (Osphena): 1 tablet orally daily
      (a) Indicated for the treatment of moderate to severe dyspareunia or vaginal dryness caused by vulvar and vaginal atrophy of menopause.
      (b) Agonist on endometrial lining affects uterine endometrium; it is recommended that women with a uterus add a progestin to any agent with estrogenic properties, although clinical studies with ospemifene alone did not find an increased risk of endometrial hyperplasia. No studies are available evaluating the use of ospemifene with a progestin.

(c) Adverse reactions (greater than 1%)
(1) Hot flashes
(2) Muscle cramps
(3) Vaginal discharge
(4) Hyperhidrosis
(d) Dose: 60 mg/day orally
(e) Contraindications similar to those of estrogen (e.g., history of estrogen-dependent cancer, undiagnosed vaginal bleeding)
(1) Pregnancy, nursing, pediatrics
(2) History of VTE
(3) Severe hepatic impairment (Child-Pugh class C)
(f) Drug interactions
(1) Rifampin decreases ospemifene exposure by 59%, and they should not be used together.
(2) Fluconazole increased ospemifene concentrations 2.7-fold and should not be used concomitantly; ketoconazole increases ospemifene 1.4-fold.
(3) Highly protein bound, about 99%; may affect other medications that are protein bound.
(4) Should not be given with estrogen products, including other selective estrogen receptor modulators.

ii. Conjugated estrogens 0.45 mg plus bazedoxifene 20 mg oral tablets (Duavee); 1 tablet orally daily (see Osteoporosis section in text that follows for more information)
(a) Indicated for treatment of moderate to severe vasomotor symptoms, prevention of osteoporosis.
(b) Selective estrogen receptor modulator used instead of a progestin (estrogen plus selective estrogen receptor modulator is called tissue selective estrogen complex).
(c) May be used in women with intact uteruses.
(d) May increase risk of DVT; should not be used in women with a history of blood clots; has contraindications similar to those of estrogen.
(e) Common adverse effects: Muscle spasms; nausea and vomiting; throat, neck, or upper abdominal pain; and indigestion

e. Prasterone vaginal insert (Intrarosa)
i. Indicated for the treatment of moderate to severe dyspareunia due to vulvar and vaginal atrophy resulting from menopause.
ii. Inactive endogenous steroid that is converted into androgens and/or estrogens. Mechanism of action is not fully understood.
iii. Administration: Vaginal insert of prasterone 6.5 mg placed vaginally once at bedtime
iv. Should not be used in women with current or past history of breast cancer; contraindicated in women with undiagnosed genital bleeding.
v. Common adverse effects: Vaginal discharge and abnormal pap smear
vi. May be stored in refrigerator or at room temperature.

f. Other hormone products
i. Bioidentical hormones: May still have adverse effects similar to those of conjugated/esterified estrogens and synthetic progestins.
ii. Androgens: Testosterone may help with sexual dysfunction but not vasomotor symptoms; not approved for use.
iii. Phytoestrogens (see text that follows for soy isoflavones): Act similarly to estrogen and carry similar contraindications.
iv. Megestrol (progestogen; see earlier section on progestogens)

3. Serotonin reuptake inhibitors: Best for vasomotor symptoms in high-risk women for whom HT is not recommended.
    a. Paroxetine 7.5 mg orally once daily (Brisdelle marketed product; only selective serotonin reuptake inhibitor with indication for vasomotor symptoms)
    b. Venlafaxine 75 mg orally once daily
    c. Fluoxetine 20 mg orally once daily
    d. Paroxetine 20 mg orally once daily
    e. Sertraline 100 mg orally once daily
    f. Escitalopram 10–20 mg orally once daily
    g. Citalopram 10–20 mg orally once daily
    h. Desvenlafaxine 100–150 mg orally once daily
4. Natural products: Some data for effectiveness (no U.S. Food and Drug Administration [FDA] indication)
    a. Soy isoflavones: May still have adverse effects similar to those of conjugated estrogens.
    b. Evening primrose oil: No solid evidence for use.
    c. Black cohosh: Some effectiveness for vasomotor symptoms; reports of liver toxicity.
5. Others: Used for vasomotor symptoms (no FDA indication) (Int J Womens Health 2012;4:305-19)
    a. Clonidine
    b. Gabapentin
    c. Pregabalin
    d. Acupuncture
    e. Hypnosis
    f. Lifestyle changes

Patient Case

Questions 1 and 2 pertain to the following case:

E.L. is a 50-year-old woman with hot flashes and vaginal irritation. She has tried exercise, diet, and antidepressants to help relieve her hot flashes but has been unsuccessful. She is otherwise healthy with no history of cancer and no surgical procedures. She states that her hot flashes are interfering with her daily activities and wants to try HT.

1. When counseling E.L. on the use of HT and explaining the WHI trial, which is best to mention, and has been proved statistically significant with, conjugated estrogen and medroxyprogesterone acetate?
    A. Increased risk of DVT
    B. Decreased risk of stroke
    C. Decreased risk of MI
    D. Increased risk of fractures

2. Which treatment is best to recommend to E.L.?
    A. Estrogen patch 0.025 mg (17β-estradiol); change patch twice weekly.
    B. Prasterone 6.5mg vaginal inserts; insert vaginally once daily.
    C. Conjugated estrogen 0.3 mg/medroxyprogesterone acetate 1.5 mg; take 1 tablet daily.
    D. Ospemifene 60 mg; take 1 tablet daily.

II. OSTEOPOROSIS

A. World Health Organization (WHO) Definitions Based on T-scores (T-score indicates that for every standard deviation [SD] below the mean young adult bone mineral density [BMD], fracture risk increases 2-fold)
   1. Normal = BMD within 1 SD of the young adult mean.
   2. Low bone mass (osteopenia) = BMD 1–2.5 SD below the young adult mean (often seen as T-score between -1 and -2.5).
   3. Osteoporosis = BMD at least 2.5 SD below the young adult mean (often seen as T-score of less than -2.5).
   4. Severe or established osteoporosis = BMD 2.5 SD below the young adult mean (often seen as T-score less than -2.5) with a fragility fracture

B. Guidelines were updated by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2020 Update. Additional guidelines that influence osteoporosis care include the 2012 American College of Obstetricians and Gynecologists (ACOG) Clinical Management of Osteoporosis, the 2010 North American Menopause Society (NAMS) Position Statement on the Management of Osteoporosis in Postmenopausal Women, the Clinician's Guide to Prevention and Treatment of Osteoporosis by the National Osteoporosis Foundation (NOF) dated 2014, the Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society (ES) Clinical Guideline dated 2019, Osteoporosis in Men and the American College of Physicians 2017 Clinical Guideline, Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians (ACP).
   1. Risk factors for osteoporotic fractures
      a. Female sex
      b. White race
      c. Poor nutrition, long-term low-calorie intake
      d. Early menopause (before age 45 (before age 40 based on AACE/ACE)) or prolonged premenopausal amenorrhea
      e. Estrogen deficiency
      f. Drugs: glucocorticoids, heparin, anticonvulsants, excessive levothyroxine, gonadotropin-releasing hormone (GnRH) agonists, lithium, cancer drugs
      g. Low body mass index (BMI) or low weight
      h. Family history of osteoporosis
      i. Low calcium and vitamin D intake
      j. Sedentary lifestyle, decreased mobility
      k. Cigarette smoking
      l. Alcoholism
      m. Dementia
      n. Impaired eyesight despite adequate correction
      o. Previous fractures
      p. History of falls
   2. Recommendations
      a. Advise patient to avoid smoking and to consume only moderate amounts of alcohol.
      b. Encourage regular weight-bearing and muscle-strengthening exercise.
      c. Encourage adequate intake of calcium (at least 1000 mg/day) and vitamin D (800–1000 international units/day) according to the NOF guidelines, or 600 international units/day for those younger than 70 years and 800 international units/day for 70 years or older according to the Institute of Medicine (IOM).

d. Assessment
   i. Dual-energy x-ray absorptiometry (DXA): Gold standard, measures hip or lumbar spine BMD
   ii. Quantitative computed tomography (QCT): Measures volumetric BMD of lumbar spine
   iii. Peripheral DXA (pDXA) and peripheral QCT (pQCT): Not appropriate for monitoring
   iv. Vertebral imaging: Used to identify vertebral fractures because they are often asymptomatic
      (a) All women 70 years or older and men 80 years or older with BMD T-score of –1.0 or less at spine, total hip, or femoral neck
      (b) Women 65–69 years and men 70–79 years if BMD T-score is –1.5 or less at spine, total hip, or femoral neck
      (c) Postmenopausal women or men 50 and older with the following risk factors:
         (1) Low-trauma fracture as an adult (age 50)
         (2) Historical height loss of 1.5 inches (4 cm) or more (since peak in adulthood)
         (3) Prospective height loss of 0.8 inches (2 cm) or more (measured at medical assessments)
         (4) Recent or ongoing long-term glucocorticoid treatment
      (d) Follow-up needed only if new back pain or further height loss is documented
   v. Clinical screening tools
      (a) FRAX score items (www.sheffield.ac.uk/FRAX/tool.jsp)
         (1) Used to estimate fracture risk
         (2) Most useful to estimate for patients with low BMD of hip
         (3) Recommended for postmenopausal women and men 50 years or older
         (4) Useful to determine whether patients with low bone mass (osteopenia) need pharmacologic treatment
         (5) Not validated for patients on drug therapy for osteoporosis
         (6) No data to show benefit in fracture reduction based on use for treatment decisions.
      (b) Other screening tools
         (1) Simple Calculated Osteoporosis Risk Estimation (SCORE)
         (2) Osteoporosis Risk Assessment Instrument (ORAI)
         (3) Osteoporosis Index of Risk (OSIRIS)
         (4) Osteoporosis Self-Assessment Tool (OST)

e. Recommended BMD testing
   i. All women 65 years and older (NAMS, ACOG, AACE/ACE, NOF), men older than 70 (NOF, ES). The USPSTF recently released a statement on osteoporosis screening for the prevention of fractures and confirmed this recommendation for women but stated that evidence was insufficient for weighing the risk-benefit for screening in men (JAMA 2018;319:2521-31).
   ii. Men 50–69 years of age with previous fractures or risk factors such as delayed puberty, hypogonadism, hyperparathyroidism, hyperthyroidism, or chronic obstructive pulmonary disease; drugs such as glucocorticoids or GnRH agonists; alcohol abuse or smoking; or other causes of secondary osteoporosis (ES)
   iii. All postmenopausal women with medical causes of bone loss (NAMS)
   iv. Postmenopausal women younger than 65 years with at least one of the following:
      (a) Previous fracture after menopause other than skull, facial bone, ankle, finger, or toe; thinness (body weight less than 127 lb [58 kg] or BMI less than 21 kg/m^2); history of hip fracture in a parent; current smoking; rheumatoid arthritis, alcohol intake of 2 units/day or more (1 unit = 12 oz beer, 4 oz wine, 1 oz liquor) (NAMS)
      (b) With any risk factor listed in section B1 (ACOG)
      (c) Previous fracture not caused by severe trauma after age 40–45 (AACE/ACE)
      (d) Thinness (body weight less than 127 lb [58 kg]), family history of spine or hip fracture (AACE)

(e) Low bone mass (osteopenia) identified radiographically (AACE/ACE)
(f) Starting or taking long-term systemic glucocorticoids for 3 months or longer (AACE/ACE, NOF)
(g) USPSTF statement recommends use of a clinical tool for screening (FRAX, SCORE, OST, ORAI, or OSIRIS) in women to determine whether BMD assessment is necessary (JAMA 2018;319:2521-31).

Table 7. 2020 AACE/ACE Criteria for Diagnosis of Osteoporosis in Postmenopausal Women

T-score -2.5 or below (lumbar spine, femoral neck, total proximal femur, or 1/3 radius)
Low-trauma spine or hip fracture (regardless of bone mineral density)
T-score between -1.0 and -2.5 **and** a fragility fracture (proximal humerus, pelvis, distal forearm)
T-score between -1.0 and -2.5 **and** high FRAX fracture probability

FRAX = Fracture Risk Assessment Tool.

f. Initiation of drug therapy (AACE/ACE, NOF, NAMS, ES)
   i. If hip or spine fracture
   ii. If BMD T-score is -2.5 or below at spine, hip, or femoral neck
   iii. If BMD T-score is between -1.0 and -2.5 at the femoral neck or spine and the 10-year probability of hip fracture is 3% or greater, or the 10-year probability of major osteoporosis-related fracture is 20% or greater, according to the FRAX system
g. Length of drug therapy: American College of Physicians recommends 5 years of pharmacologic therapy for women with osteoporosis.
h. Recommendations for follow-up on BMD-DXA vary. The 2020 AACE/ACE guidelines discuss using bone turnover markers (BTMs) (e.g., propeptide of type 1 collagen [P1NP] for bone formation; C-terminal telopeptide type 1 collagen [CTX] for bone resorption) to assess treatment adherence and efficacy. A recent fracture can cause a transient elevation in BTM. Most recent ACP guidelines recommend against monitoring BMD while on 5-year osteoporosis therapy. Other recommendations suggest follow up on BMD-DXA every 2 years. Some situations may warrant a follow-up BMD sooner than 2 years. The interval may be longer in patients with T-scores in the normal or upper bone mass range who do not have major risk factors.

C. Osteoporosis Treatments
   1. Bisphosphonates (Table 8)
      a. Alendronate (Fosamax, Binosto, Fosamax Plus D), risedronate (Actonel, Atelvia), ibandronate (Boniva), zoledronic acid (Reclast)
      b. Inhibits normal and abnormal bone resorption
      c. First-line therapy; exception: Ibandronate second-line therapy
      d. Efficacy: Reduces vertebral and non-vertebral fractures by 30%–50% (see individual agents; exception: Ibandronate reduces only vertebral fractures)
      e. Adverse events (not dose-dependent)
         i. Gastrointestinal (GI): Flatulence, acid regurgitation, esophageal ulcer, dysphasia, abdominal distention, gastritis. To reduce the risk of GI adverse effects, those taking oral bisphosphonates should not lie down for 30–60 minutes after taking the dose.
         ii. Miscellaneous: Headache, musculoskeletal pain, rash
         iii. Laboratory values: Decreases in serum calcium concentrations; decreases in serum phosphorus concentrations in the first month.

iv. Osteonecrosis of jaw: Most are associated with dental procedures. Most cases occur in patients with cancer after prolonged therapy. High-dose intravenous administration (usually for cancer-related issues) has a greater risk than oral therapy.
v. Atypical fractures and esophageal cancer: The FDA is monitoring these adverse drug reactions; for now, the recommendation is to continue use as directed by physician.
vi. Atrial fibrillation: Possible increased risk of atrial fibrillation but not of stroke or cardiovascular mortality (Chest 2013;144:1311-22). One meta-analysis showed no increased risk of stroke, myocardial infarction, total cardiovascular events or death (PLoS One 2015;10:e0122646).

f. Drug holidays are controversial; bone density may decrease 5 years after discontinuation of bisphosphonate therapy, but risk of hip fracture stays the same; however, higher risk of vertebral fracture may occur.
i. American Society for Bone and Mineral Research recommends that, after 5 years of oral bisphosphonate use or 3 years of intravenous treatment, women be reassessed for risk.
ii. Women at a high risk of fractures should continue oral therapy for up to 10 years and up to 6 years with intravenous therapy with intermittent follow-up (AACE/ACE).
iii. Women whose fracture risk decreased after 3–5 years of use should stop treatment for 2–3 years (J Bone Miner Res 2016;31:16-35).

g. Drug-food interactions: Wait at least 30 minutes after taking bisphosphonate before taking any medications, food, or drinks except for water. Exceptions: oral ibandronate (must wait 60 minutes), risedronate sodium, delayed release (Atelvia must be taken with food.)

h. Dosage for osteoporosis
i. Alendronate: 10 mg/day or 70 mg/week. Alendronate (daily dose regimen) was shown to decrease vertebral fractures by 47% and hip fractures by 51% (Fracture Intervention Trial [FIT]) in women with previous fractures.
ii. Alendronate with vitamin D: 70 mg/week with 2800 international units of vitamin D_3 or 70 mg/week with 5600 international units of vitamin D_3
iii. Alendronate 70-mg effervescent tablet/week (Binosto): Dissolve tablet in 4 oz water, wait for about 5 minutes for effervescence to stop, stir for 10 seconds, and drink contents. Has similar recommendations of waiting 30 minutes before eating or drinking and staying upright for at 30 minutes after administration.
iv. Risedronate: 5 mg/day or 35 mg/week or 150 mg once monthly. Decreases non-vertebral fracture risk by 33%–39% and vertebral fracture by 41%–49%
v. Ibandronate: 150 mg once monthly orally, waiting at least 60 minutes before eating, drinking, or taking another drug, or 3 mg intravenously every 3 months. Increases BMD at spine and hip; however, studies show only a decreased risk of vertebral fractures.
vi. Zoledronic acid: 5 mg intravenously annually for treatment and every 2 years for prevention (infuse over a minimum of 15 minutes); reduces non-vertebral fracture risk by 25%, hip fracture by 40%, and vertebral fracture risk by 70%. Lack of GI adverse effects; higher risk of atrial fibrillation with zoledronic acid than with placebo (1.3% vs. 0.4%); hypocalcemia may occur; patient must take calcium and vitamin D supplements. Infusion reactions occur, necessitating pretreatment with acetaminophen. Shown to decrease mortality in high-risk patients who have had a hip fracture (only bisphosphonate shown to decrease mortality)

i. Renal impairment as outlined in Table 8

Table 8. Bisphosphonates

Drug	Indications	Osteoporosis Dosing and Routes
Alendronate (Fosamax, Binosto) Alendronate + vitamin D_3 (Fosamax Plus D)	Prevention and treatment of osteoporosis in postmenopausal women, increase BMD in men, glucocorticoid-induced osteoporosis Paget disease	10 mg PO daily 70 mg PO weekly, 70-mg effervescent tablet PO weekly 70 mg PO weekly + vitamin D_3 2800 international units/wk or 5600 international units/wk 5 mg PO daily for prevention 35 mg PO weekly for prevention Not recommended for CrCl < 35 mL/min/1.73 m^2
Risedronate (Actonel) Risedronate delayed release (Atelvia)	Prevention and treatment of osteoporosis in postmenopausal women, increase BMD in men, glucocorticoid-induced osteoporosis Paget disease	5 mg PO daily 35 mg PO weekly (delayed release available also) 150 mg PO monthly Not recommended for CrCl < 30 mL/min/1.73 m^2
Ibandronate (Boniva)	Prevention and treatment of osteoporosis in women	2.5 mg PO daily 150 mg PO monthly 3 mg IV every 3 mo Not recommended for CrCl < 30 mL/min/1.73 m^2
Zoledronic acid (Reclast)	Prevention and treatment of osteoporosis in postmenopausal women, increase BMD in men, glucocorticoid-induced osteoporosis Paget disease	5 mg IV yearly 5 mg IV every 2 yr (prevention in women) Not recommended for CrCl < 35 mL/min/1.73 m^2

BMD = bone mineral density; CrCl = creatinine clearance; IV = intravenously; PO = by mouth

2. Denosumab (Prolia): Approved for postmenopausal women with osteoporosis at high risk of fracture, for increasing bone mass in men with osteoporosis, for treatment of glucocorticoid-induced osteoporosis, and for men and women with bone loss associated with prostate or breast cancer.
    a. Inhibits osteoclast-mediated bone resorption, monoclonal antibody against receptor activator of nuclear factor κ β ligand (RANKL), cytokine essential for formation, function, survival of osteoclasts
    b. Considered alternative first-line therapy by AACE and ACP guidelines.
    c. Administered as 60 mg subcutaneously every 6 months
    d. Not contraindicated in patients with renal dysfunction.
    e. Efficacy
        i. Increased hip (6%) and spine (9%) BMD
        ii. Reduced spinal fracture risk by 68%, hip fracture risk by 40%
    f. Safety issues
        i. Possible opportunistic infections, skin infections such as cellulitis
        ii. Hypocalcemia: Patients should take calcium and vitamin D together with denosumab. Those with impaired renal function are more likely to have hypocalcemia.
        iii. The FDA has Risk Evaluation and Mitigation Strategies (REMS) requirements for this drug (Medication Guide).

3. Calcium
    a. Recommended for all patients with osteoporosis to maintain normal calcium concentrations and to prevent hypocalcemia associated with other drug treatments for osteoporosis
    b. Elemental calcium intake: Avoid doses higher than 2500 mg/day; NOF recommends no more than 1200–1500 mg/day. Higher doses may increase risk of constipation, contribute to kidney stones, and inhibit absorption of zinc or iron (Table 9).
    c. Most common forms: Calcium carbonate (take with food), calcium citrate (take with or without food, may be good option for patients taking antacids or acid-suppressive therapy or for patients with achlorhydria)

Table 9. Recommended Daily Calcium Intake

Age Group	Recommended Daily Calcium Intake (mg)
19–50 yr: Women 51–70 yr: Men	1000
≥ 51 yr: Women ≥ 71 yr: Men	1200

4. Vitamin D
    a. Recommended for all patients with osteoporosis; promotes calcium reabsorption.
    b. Minimum dose is 800 international units/day for those older than 70 years, 600 international units/day 70 years of age and younger (IOM recommendations 2010); NOF recommendations are 800–1000 international units/day for those 50 and older.
    c. Higher doses of vitamin D may be necessary for those with vitamin D concentrations less than 30 ng/mL.
    d. Goal: 30 ng/mL in adults (NOF), although the IOM states that concentrations of 20 ng/mL may be adequate for most of the population.
5. Selective estrogen receptor modulators
    a. Raloxifene (Evista)
        i. Indication: Prevention and treatment of osteoporosis in postmenopausal women
        ii. Mechanism: Selective estrogen receptor modulator
            (a) Reduction in resorption of bone.
            (b) Decrease in overall bone turnover.
            (c) Data suggest estrogen antagonist in uterine and breast tissue.
        iii. Efficacy
            (a) Reduces the risk of vertebral fractures; (30%–50%); has not been shown to decrease hip fractures.
            (b) Lowers total cholesterol by 7% and LDL by 11%; does not reduce risk of CHD.
        iv. Adverse reactions
            (a) Hot flashes: 6%–25%
            (b) Leg cramps: 6%
            (c) VTE: About 1% (hazard ratio 2.4; 95% confidence interval, 1.2–4.5; two- to threefold increased risk compared to placebo)
        v. Dose: 60 mg/day orally
        vi. Contraindications
            (a) Pregnancy, nursing, pediatrics
            (b) History of VTE events; greatest risk of VTE events occurs during first 4 months.

vii. Drug interactions
(a) Bile acid resins decrease raloxifene absorption by 60%.
(b) Warfarin: Prothrombin time is decreased by 10%.
(c) Thyroid hormones: Separate administration by 12 hours.

b. Conjugated estrogens and bazedoxifene (Duavee)
i. Indication: Prevention of osteoporosis in postmenopausal women
ii. Mechanism: Selective estrogen receptor modulator plus estrogen (tissue-selective estrogen complex [TSEC])
iii. Efficacy
(a) Significantly increased total hip BMD at 24 months by 1.96% compared with placebo in women who had been postmenopausal for 1–5 years and by 1.73% in women who had been postmenopausal for more than 5 years.
(b) Significantly increased mean lumbar spine BMD (by 1.51%) compared with placebo at 12 months in women who had been postmenopausal for 1–5 years.
iv. Adverse reactions (5% or more)
(a) Hot flashes
(b) Muscle cramps
(c) Throat, neck, and muscle pain
(d) Dizziness
(e) Nausea and vomiting
v. Dose: Conjugated estrogen 0.45 mg and bazedoxifene 20 mg/day orally
vi. Contraindications
(a) Pregnancy, nursing, pediatrics
(b) History of VTE events or coagulopathy
(c) Hepatic impairment
(d) Similar to estrogen contraindications
vii. Drug interactions: Metabolized by cytochrome P450 (CYP) 3A4; inducers or inhibitors of CYP3A4 may affect estrogen concentrations.

6. Human parathyroid hormone related peptide analogs
a. Teriparatide (Forteo)
i. Recombinant human parathyroid hormone regulates bone metabolism, intestinal calcium absorption, and renal tubular calcium and phosphate reabsorption.
ii. Indications: Treatment of postmenopausal women with osteoporosis that have a high risk of fracture, increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
iii. Efficacy
(a) Reserved for treating women at high risk of fracture, including those with very low BMD (T-score lower than –3.0) and a previous vertebral fracture.
(b) Decreases vertebral fractures by 65% and non-vertebral fractures by 53%; not shown to decrease hip fractures.
iv. Contraindications: Hypercalcemia, bone metastases, disorders that predispose women to bone tumors such as Paget's disease
v. Adverse effects: Nausea, orthostatic hypotension
vi. Carcinogenicity: Osteosarcoma in rats; should not be used longer than 2 years.
vii. Drug interactions: Increases calcium concentrations and may increase risk of digoxin toxicity.
viii. Dosage: 20 mcg/day subcutaneously

b. Abaloparatide (Tymlos)
    i. Regulates bone metabolism, intestinal calcium absorption, and renal tubular calcium and phosphate reabsorption.
    ii. Indication: Treatment of postmenopausal women with osteoporosis that have a high risk of fracture.
    iii. Efficacy
        (a) Reserved for treating women at high risk of fracture, including those with very low BMD (T-score lower than –3.0) and a previous vertebral fracture.
        (b) Decreases vertebral fractures by 86% and non-vertebral fractures 43%; not shown to decrease hip fractures.
    iv. Contraindications: None
    v. Precautions: Orthostatic hypotenstion: patient should be instructed to sit or lay down if symptoms occur post dose administration; hypercalcemia: avoid in patients at risk for hypercalcemia; hypercalciuria and urolithiasis: monitor urine calcium if patient experiences symptoms.
    vi. Adverse effects: Nausea, dizziness, headache, palpitations, hypercalciuria, upper abdominal pain and vertigo
    vii. Carcinogenicity: Osteosarcoma in rats; should not be used longer than 2 years.
    viii. Drug interactions: Increases calcium concentration and may increase risk of digoxin toxicity.
    ix. Dosage: 80 mcg/day subcutaneously; patients should also take supplemental calcium and vitamin D if dietary intake is not enough.

7. Romosozumab-aqqg (Evenity)
    a. Sclerostin inhibitor, a factor in bone regulation, helps build bone and decreases bone resorption.
    b. Indication: Treatment of osteoporosis in postmenopausal who are at high risk of fracture (defined as a history of osteoporotic fracture or several risk factors for fracture) or for those whose other osteoporosis treatments have failed
    c. Efficacy: In a study of more than 7000 women, romosozumab decreased the absolute risk of new vertebral fracture by 1.3% at 12 months (fracture risk in placebo group 1.8% vs. 0.5% in treatment group, p<=0.001) and by 1.9% at 24 months (fracture risk in placebo group 2.5% vs. 0.6% in treatment group, p=<0.001); increased BMD by 12.7% at lumbar spine, 5.8% at total hip, 5.2% at femoral neck
    d. Contraindications: Hypocalcemia, sensitivity to romosozumab
    e. Precautions: Major adverse cardiac events (MI, stroke); hypocalcemia; hypersensitivity (e.g., allergic reaction, angioedema); osteonecrosis of the jaw and atypical femoral fracture
    f. Adverse effects: Joint pain and headache
    g. Carcinogenicity: None reported
    h. Dosages: Dose of 210 mg injected subcutaneously once a month for 12 months. May be injected in abdomen, thighs, or upper arm. Need to have 2 injections to achieve the dose of 210 mg (give one after the other). Patients should also take supplemental calcium and vitamin D if dietary intake is not enough. No dosage adjustments for renal impairment; however, in patients receiving dialysis or who have a creatinine clearance (CrCl) less than 29 mL/minute/1.73 m_2, may increase the risk of hypocalcemia

8. Calcitonin-salmon (Miacalcin)
    a. Inhibition of bone resorption
    b. Indicated for treatment of osteoporosis in women who are more than 5 years postmenopause.
    c. Not a first-line drug; useful for bone pain caused by vertebral compression fractures, no longer used frequently for osteoporosis therapy.
    d. Efficacy: Nasal calcitonin reduces the incidence of new vertebral fractures by 36%.
    e. Adverse effects
        i. Nasal (10%–12%): Rhinitis, epistaxis, irritation, nasal sores, dryness, tenderness
        ii. Other (3%–5%): Backache, arthralgia, headache

f. Drug interactions: None
g. Dosage: 200 international units/day in one nostril, alternating nostrils daily
   i. 200 international units nasally = 50–100 international units by injection
   ii. 200 international units per actuation, so one bottle will last about 2–3 weeks
h. FDA labeling changes regarding safety in 2014: Malignancies reported to be higher in those treated with calcitonin than in those treated with placebo. Benefits for patient should be discussed with patient and carefully considered.

9. Menopausal estrogen therapy or menopausal estrogen and progestogen therapy; (see Hormone Therapy and Menopause section earlier)
10. Lifestyle modifications
    a. Weight-bearing exercise that includes walking, tai chi, dancing, and tennis; recommend 30–40 minutes per session most days of the week, if possible; helps maintain bone strength.
    b. Smoking cessation: Smokers tend to have lower BMD scores than nonsmokers and may reach menopause earlier.
    c. Limiting alcohol intake: Affects fall risk; 2 or more units of alcohol per day associated with 20% of falls at home, according to one study. No more than 2 units/day or 7 units/week is recommended.
    d. Fall prevention

Table 10. Postmenopausal Osteoporosis Treatment

High Risk/No Prior Fractures			
First Line	**Alternative First Line**	**Increasing or Stable BMD and No Fractures**	**Progression of Bone Loss or Recurrent Fractures**
Alendronate, denosumab, risedronate, zoledronate	Ibandronate, raloxifene	Drug holiday (after 5 yr of PO or 3 yr of IV therapy) Resume therapy with a fracture, BMD declines, BTM rises to pretreatment value	Assess adherence Change to injectable antiresorptive (if on PO) If on injectable or at very high risk, change to abaloparatide, romosozumab, or teriparatide
Very High Risk/Prior Fractures			
First Line			**Alternative First Line**
Denosumab – continue until no longer high risk; transition to another antiresorptive agent Romosozumab × 1 yr – sequential therapy with PO or injectable antiresorptive agent Abaloparatide or teriparatide × 2 yr – sequential therapy with PO or injectable antiresorptive agent Zoledronate × 6 yr (if stable) – if progressive bone loss or recurrent fractures, change to abaloparatide, teriparatide, or romosozumab			Alendronate, risedronate

BMD = bone mineral density; BTM = bone turnover marker.

Patient Case

Questions 3 and 4 pertain to the following case:

R.K. is a 71-year-old white woman (height 63 inches, weight 64 kg) with a history of rheumatoid arthritis who smokes ½ pack/day. She is lactose intolerant and has minimal intake of dairy products. She takes calcium 1200 mg orally per day in divided doses and vitamin D 600 international units/day orally. Her calculated CrCl is 60–70 mL/minute/1.73 m^2. Her BMD T-score is -2.6 at the hip and -2.1 at the spine. Her FRAX score indicates she has a 10-year probability of a major osteoporotic fracture of 22% and a 10-year probability of a hip fracture of 11%.

3. Which statement best describes the correct diagnosis for R.K.?
   A. She has normal BMD of the spine.
   B. She has low bone mass (osteopenia) of the hip.
   C. She has osteoporosis of the hip.
   D. She has severe osteoporosis of the spine.

4. Which is the best therapy for R.K.?
   A. No further treatment is needed; continue calcium 1200 mg/vitamin D 600 international units/day orally.
   B. Give abaloparatide 80 mcg subcutaneously daily, and continue calcium 1200 mg/vitamin D 600 international units/day orally.
   C. Give romosozumab 210 mg subcutaneously every month, continue calcium 1200 mg/day orally, and increase vitamin D to 800 international units/day orally.
   D. Give risedronate 35 mg orally every week; continue calcium 1200 mg orally per day, and increase vitamin D to 800 international units/day orally.

III. DRUGS IN PREGNANCY

A. Definitions and Overview
   1. Teratogen: Drug or environmental agent with the potential to cause abnormal fetal growth and development
   2. Teratogenicity: Capability of producing congenital abnormalities, major or minor malformations

B. Causes of Defects
   1. Genetic predisposition 25%
   2. Drug 2%–3%
   3. Unknown 72%–73%

C. Factors That Influence Risk of Medication Use in Pregnancy
   1. Genotypes of mother and fetus
   2. Embryonic stage at exposure
   3. Medication dose
   4. Simultaneous exposure to other drugs that may increase or decrease medication concentrations
   5. Timing of exposure
      a. 1 month before conception: Folic acid 0.4 mg or more taken daily to prevent neural tube defects
      b. Around time of conception and implantation
      c. First 12–15 days after conception: If one cell is damaged, another can assume its function.
      d. First 3 months: Physical malformations

e. Throughout pregnancy: Functional and behavioral defects because brain development occurs throughout pregnancy.

6. Factors for placental transport
   a. Molecular weight of drug less than 400–600 Da crosses placenta; most drugs weigh 250–400 Da.
   b. Degree of protein binding; lower in fetus, so more free-drug concentration.
   c. Maternal and fetal blood flow usually equivalent; simple diffusion allows fetal drug concentration to be 50%–100% of maternal.
   d. Metabolic activity of the placenta; excretion of medications by the fetus occurs in liver and placenta.

D. Risk Factor Categories
   1. In 1979, the FDA introduced risk categories for drugs used during pregnancy.
   2. The FDA pregnancy risk categories appear in Box 1.

Box 1. Previous FDA Pregnancy Risk Categories

A: Controlled studies of women fail to show risk.
B: Animal studies indicate no risk, or animal studies show a risk that has not been shown in human studies.
C: No available studies of women or animals, or animal studies have shown a risk.
D: Positive evidence of fetal risk.
X: Definite fetal risk in animals or women.

   3. The FDA decided current pregnancy risk categories were inadequate; therefore, in 2008 the FDA recommended a new labeling system that became effective June 30, 2015 that includes the following:
      a. Pregnancy (includes labor and delivery)
         i. Fetal risk summary
         ii. Clinical considerations
         iii. Data section
         iv. Information for exposure registries
      b. Lactation
      c. Females and males of reproductive potential

E. Factors to Consider When Initiating Medications in Pregnant Women (Boxes 2, 3, 4, and 5)
   1. Risk-benefit ratio
   2. Is drug necessary?
   3. Most effective agent with least risk
   4. Lowest effective dosage for shortest possible duration
   5. Health of mother without drug

Box 2. Selected Known Teratogens

Alcohol	Mercury
Androgens	Methimazole
Angiotensin-converting enzyme inhibitors	Methotrexate
Angiotensin II receptor blockers	Paroxetine
Anticonvulsants	Penicillamine
Antineoplastics	Statins
Cocaine	Tetracyclines
Diethylstilbestrol	Thalidomide
Fluconazole (high doses)	Vitamin A (higher than recommended daily doses)
Iodides	Warfarin
Isotretinoin	
Lead	
Lithium	

Box 3. Examples of Drugs Used in Pregnancy (if benefit outweighs risk)

Acetaminophen
Cephalosporins
Cetirizine
Erythromycin
Penicillin
Pyridoxine/doxylamine

Box 4. Some Drugs with Known Pregnancy Risks: Should Be Used with Caution

Aminoglycosides	Diuretics
Antithyroid drugs	Isoniazid
Aspirin	Narcotic analgesics (chronic)
Barbiturates	Nicotine
Benzodiazepines	NSAIDs
Caffeine	Oral hypoglycemics
Chloramphenicol	β-Blockers

NSAIDs = nonsteroidal anti-inflammatory drugs

Box 5. Types of Adverse Effects After Fetal Drug Exposure

Cancer	Renal dysfunction
Developmental delay or deficiency	Seizures
Fetal death	Sexual or reproductive dysfunction
Growth retardation	Teratogenic abnormalities
Hematologic abnormalities	Thyroid dysfunction
Low birth weight for gestational age	Withdrawal
Metabolic abnormalities	

F. Resources for Medication Use During Pregnancy
   1. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. Philadelphia: Wolters Kluwer, 2017.
      a. Available as a textbook or online by subscription to Facts & Comparisons eAnswers online and Lexi-Comp.
      b. Provides information about medication use during pregnancy and lactation.
   2. TERIS (Teratogen Information System, http://depts.washington.edu/terisdb/) and Shepard's Database
      a. Available on its own by subscription or by a subscription to Micromedex Solutions.
      b. Provides access to the Clinical Teratology Web (http://depts.washington.edu/terisdb/terisweb/index.html) and has a list of several textbook references and websites not all listed here.
   3. Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians. Bethesda, MD: American Society of Health-System Pharmacists, 2009.
      a. Available as a textbook.
      b. Provides information on chronic disease management in pregnancy.
   4. Organization of Teratology Information Specialists (OTIS): MotherToBaby (http://mothertobaby.org/)
      a. Available online by subscription.
      b. Has some resources available to public and providers such as information sheets.
      c. Free hotline for questions (866-626-6847) or e-mail an expert.
   5. Micromedex Solutions: REPROTEXT and REPROTOX
      a. Available by purchase.
      b. Provides information about pregnancy, teratogenicity, and lactation and medication use.

IV. DRUGS IN LACTATION

A. Drugs That Decrease Milk Supply (Box 6)

Box 6. Drugs That Decrease Milk Supply

Androgens	Monoamine oxidase inhibitors (MAOIs)
Bromocriptine	Nicotine
Ergot alkaloids	Pyridoxine
Estrogen	Sympathomimetics
Levodopa	

B. Drugs That Increase Milk Production (Galactagogues) (Box 7)

Box 7. Drugs That Increase Milk Production (Galactagogues) (may or may not be safe in breastfeeding)

Amoxapine	Methyldopa
Antipsychotics	Metoclopramide
Cimetidine	Reserpine

C. Ways to Minimize Effects of Drugs During Breastfeeding
   1. Short-term drug: Mother can pump and discard milk.
   2. Choose drugs with short half-lives.
   3. Administer drug immediately after a feeding or before a long sleep period.
   4. Consider whether the drug is given to neonates.
   5. Consider age and health status of the infant (e.g., concomitant medical conditions, preterm birth).

D. Safe and Unsafe Drugs in Breastfeeding (Boxes 8 and 9)

Box 8. Some Drugs Contraindicated in Breastfeeding According to the American Academy of Pediatrics

Amphetamines	Pain medications (common ones include oxycodone, pentazocine, and meperidine)
Antineoplastics	
Benzodiazepines	
Bromocriptine	
Cocaine	Yohimbe
Drugs of abuse	Herbs that lack safety data (chamomile, black cohosh, blue cohosh, chaste tree, echinacea, ginseng, ginkgo, St. John's wort, valerian)
Ergotamine	
Kava	
Lithium	
Nicotine	

Box 9. Relatively Safe Agents During Lactation

Analgesics (ibuprofen, acetaminophen)
Antibiotics (penicillins, cephalosporins, erythromycins)
Caffeine (in moderation [1 or 2 cups/day])
Insulin

E. Specific Resources for Drug Information Regarding Lactation
   1. LactMed (http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm)
      a. Available through the U.S. National Library of Medicine.
      b. Available without purchase or subscription.
      c. Provides information about safety of medication use during lactation and provides alternative recommendations.
   2. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. Philadelphia: Wolters Kluwer, 2017.
      a. Available as a textbook or by subscription to Facts & Comparisons eAnswers online.
      b. Provides information about medication use during pregnancy and lactation.
   3. Hale T. Medications and Mothers' Milk
      a. Available by purchase; online site: www.halesmeds.com
      b. Provides information on medication use in lactation with a scoring system of safety.
         i. L1: Safest. Drug has been taken by many breastfeeding mothers with no observed increase in adverse effects in the infant
         ii. L2: Safer. Drug has been studied in a limited number of breastfeeding women with no increase in adverse effects in the infant
         iii. L3: Moderately safe. No controlled studies in breastfeeding women; however, adverse effects in the infant are possible
         iv. L4: Possibly hazardous. Positive evidence of risk to a breastfed infant or to breast milk production
         v. L5: Contraindicated. Studies of breastfeeding mothers have shown that there is risk to the infant, or there is a high risk of causing significant harm to the infant.
   4. Micromedex solutions: REPROTEXT and REPROTOX
      a. Available by purchase.
      b. Provides information about pregnancy, teratogenicity, and lactation and medication use.
   5. Organization of Teratology Information Specialists OTIS: MotherToBaby (http://mothertobaby.org/)
      a. Available online by subscription.
      b. Has some resources available to public and providers such as information sheets.
      c. Free hotline for questions (866-626-6847) or e-mail an expert.

V. COMPLICATIONS IN PREGNANCY

A. Conditions in Pregnancy
   1. Morning sickness
   2. Heartburn
   3. Constipation
   4. Hemorrhoids
   5. Headache
   6. Coagulation disorders
   7. Gestational diabetes mellitus
   8. Pregnancy-induced hypertension
   9. Preterm labor
   10. Induction of labor

B. Morning Sickness
   1. Nausea and vomiting associated with pregnancy
   2. Usually during first trimester
   3. Usually occurs on rising and diminishes as day progresses
   4. Cause: Unknown
   5. Hyperemesis gravidarum: Severe nausea and vomiting lead to dehydration and malnutrition.
   6. Nonmedical treatment: First line
      a. Eat saltine crackers.
      b. Keep stomach from becoming completely empty.
      c. Eat small, dry meals.
      d. Avoid spicy and odorous foods.
   7. Symptomatic treatment
      a. Doxylamine and pyridoxine (Diclegis: doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg; dosage 2 tablets orally at bedtime daily. Maximum dosage: One tablet in the morning, one mid-afternoon, and two at bedtime. Bonjesta: doxylamine succinate extended release 20 mg and pyridoxine hydrochloride 20 mg; maximum dosage: 1 tablet in the morning, 1 tablet at bedtime) – considered first-line treatment after nonpharmacologic treatment.
      b. Pyridoxine: Considered first-line treatment after nonpharmacologic treatment.
      c. Meclizine
      d. Dimenhydrinate
      e. Diphenhydramine
      f. Ondansetron: Only if nausea and vomiting not controlled with first-line agents; possibility of a slight increase in cardiac birth defects, mainly septal defects, according to two studies; best to avoid, especially during first 10 weeks of gestation, if possible (Obstet Gynecol 2018;131:e15-e30).
      g. Metoclopramide – Only if nausea and vomiting not controlled with first-line agents.
      h. Phenothiazines – Only if nausea and vomiting not controlled with first-line agents.

C. Heartburn
   1. Occurs in latter half of pregnancy.
   2. Cause: Enlarged uterus puts pressure on stomach, and esophageal sphincter relaxes.
   3. Nonmedical treatment
      a. Smaller, more frequent meals
      b. Avoid food and liquids 3 hours before bed.
      c. Elevate head of bed with blocks.

4. Symptomatic relief
    a. Antacids
        i. Magnesium hydroxide
        ii. Aluminum hydroxide (overuse may lead to neurotoxicity)
        iii. Calcium carbonate
    b. Sucralfate: Not absorbed in GI tract.
    c. Second line: Histamine-2 receptor antagonists (other than ranitidine; ranitidine removed from market in April 2020), proton pump inhibitors

D. Constipation
1. Cause: Decreased peristalsis
2. Nonmedical treatment
    a. Increase high-fiber foods.
    b. Increase fluid intake to eight 8-oz glasses of water a day.
    c. Increase exercise.
3. Symptomatic relief
    a. Stool softeners (check that prenatal vitamin does not already contain docusate)
    b. Bulk laxatives: Not absorbed.
    c. Stimulants: Not recommended as first-line therapy.
    d. Avoid mineral oil: Impairs vitamin K absorption and could cause hypoprothrombinemia.

E. Hemorrhoids
1. Caused by constipation and increased venous pressure below uterus
2. Correct constipation with stool softeners, appropriate hydration, and dietary fiber.
3. Sitz baths
4. Avoid topical anesthetics and steroids, not well studied. If medication therapy is required, topical anesthetics and steroids may be used short term under a physician's direction (Can Fam Physician 2008;54:189-90).

F. Headache
1. Cause: Hormone fluctuations
2. Therapy
    a. Rest, ice packs
    b. Acetaminophen
3. Drugs to avoid
    a. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)
    b. Triptans, ergotamine

G. Coagulation Disorders
1. Anticoagulation necessary
    a. History of DVT
    b. Prosthetic heart valve
    c. Deficiencies of clotting factors
    d. Antiphospholipid antibodies
2. Therapy
    a. Avoid warfarin.
    b. Heparin or low-molecular-weight heparin (monitor for osteoporosis if heparin is used long term)
    c. Low-molecular-weight heparin preferred to heparin (Obstet Gynecol 2018;132:e18-34; Chest 2012; 141: e691S-736S).

d. Dosing
   i. Prophylactic
      (a) Enoxaparin 40 mg subcutaneously daily (ACOG and American College of Chest Physicians [ACCP])
      (b) Dalteparin 5000 units subcutaneously daily (ACOG and ACCP)
      (c) Tinzaparin 4500 units subcutaneously daily (ACOG and ACCP)
      (d) Heparin 5000–7500 units subcutaneously every 12 hours for first trimester, 7500–10,000 units subcutaneously every 12 hours for second trimester, and 10,000 units subcutaneously every 12 hours for third trimester unless activated partial thromboplastin time (aPTT) is elevated (ACOG)
   ii. Therapeutic
      (a) Enoxaparin 1 mg/kg subcutaneously every 12 hours (ACOG and ACCP)
      (b) Dalteparin 200 units/kg subcutaneously daily or 100 units/kg subcutaneously every 12 hours (ACOG and ACCP)
      (c) Tinzaparin 175 units/kg subcutaneously daily (ACOG and ACCP)
      (d) Heparin 10,000 units subcutaneously every 12 hours with target activated partial thromboplastin time (aPTT) range (1.5–2.5) 6 hours after injection (ACOG) or adjusted-dose unfractionated heparin subcutaneously every 12 hours, with mid-interval aPTT target of 2 times the control (ACCP)

e. May consider switching LMWH to heparin at 36 weeks of gestation to permit induction of neuroaxial anesthesia during labor and delivery (ACOG).
f. Prophylaxis with LMWH or UFH should be discontinued 12–24 hours before cesarean section or vaginal delivery. Therapeutic doses should be discontinued 24–36 hours before cesarean section or vaginal delivery.
g. Consider timing of catheter placement for anesthesia as well.
h. Continue anticoagulation for 6 weeks postpartum.
i. For women experiencing heparin-induced thrombocytopenia, consider fondaparinux; limited data and crosses placenta.

H. Gestational Diabetes Mellitus (GDM)
   1. Diagnostic approaches (Table 11)

Table 11. GDM Diagnostic Approaches

Approach	Criteria	Organizations	Comments
Two-step approach	50-g oral glucose test Plasma measured 1 hr after If ≥ 130 mg/dL or 140 mg/dL, give 100-g, 3-hr glucose test	ACOG, NIH	Given at 24–28 weeks' gestation; may be earlier in those with risk factors
One-step approach	Obtain A1C at initial prenatal visit; if elevated, patient has overt diabetes; no further testing 75 g oral glucose test Plasma measured at fasting, 1 and 2 hr	IADPSG, ADA	Given at 24–28 weeks' gestation

ADA = American Diabetes Association; GDM = gestational diabetes mellitus; IADPSG = International Association of the Diabetes and Pregnancy Study Groups; NIH = National Institutes of Health

2. Diagnostic criteria
    a. Two-step approach: 100-g 3-hour oral glucose test (OGTT) used after initial screening; if greater than or equal to values at two or more points, consider GDM (Table 12).

Table 12. 3-Hr Oral Glucose Test Reference Range

Time	Plasma Glucose Concentration (mg/dL) Carpenter-Coustan	Plasma Glucose Concentration (mg/dL) National Diabetes Data Group
Fasting	95	105
1 hr	180	190
2 hr	155	165
3 hr	140	145

    b. One-step approach: Based on 75-g 2-hour oral glucose test (Table 13)

Table 13. Glucose Reference Range for 2-Hr Oral Glucose Test

Time	Plasma Glucose
Fasting	92 mg/dL
1 hr	≥ 180 mg/dL
2 hr	≥ 153 mg/dL

3. Insulin (first line)
    a. Regular (most studied, drug of choice in combination with neutral protamine Hagedorn)
    b. Neutral protamine Hagedorn insulin (in combination with regular insulin, drugs of choice)
    c. Levemir – Has indication for pregnancy use.
    d. Lispro and aspart starting to be used.
4. Sulfonylureas (glyburide) in patients unable to use insulin injections; however, recent evidence shows they may be inferior to insulin and metformin because of increased risk of hypoglycemia and macrosomia in the infant. In addition, they have been shown to cross the placenta (Diabetes Care 2019;42 (suppl 1):S165-S172). ACOG recommends against use as first-line therapy stating that glyburide does not yield similar outcomes as insulin (Obstet Gynecol 2018;131:e49-64).
5. Metformin may have advantage over glyburide; studies are ongoing, (not first line), associated with some risk of premature birth and also may cross the placenta; may emerge as possible treatment, according to ACOG (Diabetes Care 2019;42(suppl 1):S165-S172; Obstet Gynecol 2018;131:e49-64).

I. Pregnancy-Induced Hypertension: Hypertension occurring after 20 weeks' gestation
1. Gestational hypertension: 140/90 mm Hg or more, occurring at least 4 hours apart on two different occasions in women with previously normal blood pressure without proteinuria or pathologic edema
2. Preeclampsia: Hypertension plus proteinuria (300 mg/dL or more every 24 hours), any other severe features of preeclampsia such as systolic blood pressure higher than 160 mm Hg or diastolic blood pressure higher than 110 mm Hg at least 4 hours apart and on two occasions (unless antihypertensive treatment was started before this time), thrombocytopenia (platelet count less than 100,000/mm^3), impaired liver function (increased levels of liver function enzymes to twice normal or severe right upper quadrant pain or epigastric pain refractory to medication and not accounted for by other diagnoses), new development of renal insufficiency (serum creatinine greater than 1.1 mg/dL or a doubling of the serum creatinine without evidence of other renal disease), pulmonary edema, new development of headache that does not respond to therapy and has no known cause, or visual changes (ACOG Chronic Hypertension in Pregnancy. Obstet Gynecol 2019;133:e26-e50; ACOG Gestational Hypertension and Preeclampsia. Obstet Gynecol 2019;133:e1-e25).

3. Eclampsia: Tonic-clonic seizures
4. Chronic hypertension: Preexisting hypertension before 20 weeks' gestation
5. Chronic hypertension with superimposed preeclampsia: New-onset proteinuria after 20 weeks, sudden 2- to 3-fold increase in proteinuria, sudden increase in blood pressure, increased aspartate transaminase–alanine transaminase, thrombocytopenia
6. Prevention: Women at high risk of preeclampsia development may take aspirin 60–80 mg beginning in late first trimester; a study showed lower incidence of preeclampsia development in women who were administered 150 mg of aspirin from 11 to 14 weeks of gestation to 36 weeks.
7. Risk of preeclampsia and aspirin use
    a. Should receive aspirin if there are several risk factors (history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or 2 diabetes, renal disease, or autoimmune disease)
    b. Consider low-dose aspirin if more than one moderate risk factor (nulliparity, BMI greater than 30 kg/m^2, family history of preeclampsia in mother or sister, sociodemographic characteristics [Black/African American, low socioeconomic status], older than 35 years, personal history of adverse pregnancy outcomes, more than a 10-year pregnancy interval)
    c. No aspirin needed (previously uncomplicated full-term pregnancy) (Obstet Gynecol 2019;133:e1-e25; NEJM June 28, 2017 Available at http://www.nejm.org/doi/pdf/10.1056/NEJMoa1704559).
8. Treatment
    a. Delivery if at term
    b. If not at term, get bed rest and monitor blood pressure.
    c. Severe preeclamptic, parenteral magnesium sulfate to prevent seizures
    d. Labetalol (oral), nifedipine (oral, extended release) are first-line therapies. Methyldopa (limited use because of adverse effects of sedation, depression, and dizziness) and hydrochlorothiazide are second- or third-line agents.
    e. Urgent blood pressure control antihypertensives: Labetalol (intravenous), hydralazine (intravenous), nifedipine (oral, immediate release; concern for serious adverse effects when used simultaneously with magnesium)
    f. Medications to avoid: Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists

J. Preterm Labor
1. Definitions
    a. Term labor: Weeks 37–40
    b. Preterm labor: Uterine contractions with cervical changes before week 37
2. Nonpharmacologic treatment
    a. Inhibition of labor not usually tried before week 20.
    b. Bed rest, hydration, and sedation
3. Prophylaxis for patients with a history of preterm labor 16–36 weeks: 17-hydroxyprogesterone acetate 250 mcg intramuscularly every week from 16 to 36 weeks' gestation
4. Tocolytic drugs (inhibit uterine contractions), especially if cervix dilated less than 4 cm and membranes intact
    a. β-Agonists
        i. Terbutaline: Often used, unlabeled use, intravenously, subcutaneously, orally
        ii. Adverse effects: Hypotension, tachycardia, hypokalemia, tremor, nervousness, angina, headache, hypoglycemia in patients with diabetes mellitus
        iii. FDA warning for intravenous use beyond 48 hours because of severe adverse effects in the mother such as elevated heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia. Warning also against use of oral terbutaline for preterm labor because of lack of efficacy.

b. Magnesium sulfate
    i. Inhibits uterine activity by antagonism of calcium.
    ii. Anticonvulsant in eclampsia.
    iii. Serum magnesium concentrations 5–8 mEq/L
    iv. May be drug of choice in patients with diabetes.
c. Prostaglandin synthetase inhibitors (NSAIDs)
    i. Prostaglandins are in amniotic fluid during labor and delivery but not during pregnancy.
    ii. Indomethacin: Oral or rectal
    iii. Adverse effects: Premature closure of ductus arteriosus, necrotizing enterocolitis, intracranial hemorrhage, renal dysfunction
    iv. Limit use to 72 hours.
d. Calcium channel blockers
    i. Calcium necessary for muscle contraction.
    ii. Nifedipine: Typically used; use caution when administered near administration of magnesium, may result in hypotension.
    iii. Verapamil: Large doses needed that mother usually cannot tolerate.

K. Induction of Labor
1. Induction indicated
    a. Severe maternal infection
    b. Uterine bleeding
    c. Preeclampsia or eclampsia
    d. Diabetes mellitus
    e. Macrosomia
    f. Maternal renal insufficiency
    g. Premature rupture of membranes after week 36
    h. Evidence of placental insufficiency
    i. Postdatism (more than 42 weeks)
2. Inducing agents
    a. Oxytocin
        i. Drug of choice for labor induction
        ii. Intravenous administration
        iii. Adverse effects: Uterine rupture, uteroplacental hypoperfusion, fetal distress from hypoxia
    b. Ergot alkaloids
        i. Not used to induce labor at term or late in pregnancy.
        ii. Violent, sustained uterine contractions
        iii. Used to terminate early pregnancy
        iv. Decrease postpartum or postabortion bleeding
        v. Oral and parenteral
    c. Prostaglandins: Used primarily for cervical ripening
        i. Dinoprostone also known as PGE2 (prostaglandin E_2)
            (a) Vaginal gel or insert, sometimes compounded suppositories
            (b) Applied to cervix
            (c) Adverse effects: Headache, nausea, vomiting, diarrhea, abdominal pain, and uterine hyperstimulation
        ii. Misoprostol (off-label use), also known as PGE1 (prostaglandin E_1)
            (a) Available orally and vaginally
            (b) Adverse effects: Headache, nausea, vomiting, diarrhea, abdominal pain, and uterine hyperstimulation

Patient Case

5. S.E. is a 28-year-old woman who would like to get pregnant soon. Her medical history includes hypertension and allergies. Her medications include lisinopril, nasal saline spray, and folic acid. Which option is best to treat her hypertension while she is pregnant or trying to conceive?

   A. Continue lisinopril and add hydrochlorothiazide.

   B. Discontinue lisinopril and all other medications.

   C. Discontinue lisinopril and start labetalol.

   D. Continue lisinopril and add atenolol.

VI. OVERVIEW OF CONTRACEPTION

A. Epidemiology
   1. About 45% of pregnancies are unintended in the United States, with about 42% of those resulting in abortions (according to 2011 data, N Engl J Med 2016;374:843-52).
   2. According to the Guttmacher Institute, about 9.7 million women in 2012 were using an oral contraceptive (OC) pill in the United States, 1.8 million were using injections, and 3.8 million were using intrauterine devices (IUDs).

B. Physiology Review: Menstrual Cycle
   1. Follicular phase: GnRH stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH); FSH stimulates estradiol secretion and stimulates follicles to develop; one in particular will become the dominant follicle; occurs in first half of cycle; later in follicular phase; LH causes an increase in androgen values.
   2. Ovulation: Occurs midcycle; mature follicle ruptures; a surge in LH occurs just before ovulation.
   3. Luteal phase: Progesterone is the more dominant hormone in the second half of cycle.
   4. Menses: Hormones have decreased, and withdrawal bleeding occurs if a woman does not become pregnant.

C. Properties Desired in Contraceptives
   1. Highly effective
   2. Prolonged duration of action
   3. Rapidly reversible
   4. Privacy of use
   5. Protection against sexually transmitted diseases
   6. Easily accessible

D. Factors in Selecting Contraception
   1. Effectiveness
      a. Theoretical: Method failure if patient uses method perfectly (e.g., combined oral contraceptive [pills] [COCs] have 99% theoretical effectiveness in preventing pregnancy)
      b. Actual: Combines method failure plus patient failure (e.g., COCs have 93% actual effectiveness when average patient use is considered).
   2. Importance of not being pregnant
   3. Likelihood and ability to adhere
   4. Frequency of intercourse: Frequent versus infrequent
   5. Age: Age may affect adherence or adverse effect risks.

6. Cost and ability to pay
7. Adverse effects
8. Perceptions, misperceptions, risk-benefit
9. Concomitant drug use
10. Health status and habits
11. Patient preference

E. Methods of Birth Control
   1. Abstinence
   2. Male or female sterilization
   3. Natural family planning
   4. Spermicides
   5. Barrier methods
      a. Diaphragm or cervical cap
      b. Condom
      c. Female condom
      d. Sponge
   6. Hormonal contraception
      a. Combined contraceptives
         i. Combined oral contraceptive (COC) pills
         ii. Transdermal patch
         iii. Vaginal ring
      b. Progestin-only
         i. Progestin-only pill (POP or minipill)
         ii. Progestin-only injectable
         iii. Implanted rod
   7. Intrauterine device (IUD) or intrauterine system (IUS)
      a. Copper IUD
      b. Progestin-containing IUD or IUS

VII. COMBINED HORMONAL CONTRACEPTIVES, CONTAINING BOTH AN ESTROGEN AND A PROGESTIN HORMONE

A. Indications
   1. FDA label approved
      a. Prevent pregnancy
      b. Acne (Estrostep Fe, Ortho Tri-Cyclen, YAZ, Beyaz)
      c. Premenstrual dysphoric disorder (YAZ, Beyaz)
   2. Off-label use
      a. Hirsutism
      b. Cycle control
      c. Headaches
      d. Premenstrual syndrome
      e. Iron-deficiency anemia
      f. Relief of menstrual cramps

B. Components
   1. Estrogen
      a. Type of estrogens available in products in the United States
         i. Ethinyl estradiol (in almost all products), estradiol valerate (Natazia only)
         ii. Mestranol (not used often)
      b. Pharmacologic actions of estrogen in contraceptives
         i. Feeds back to the pituitary, inhibiting FSH and ovulation.
         ii. Increases aldosterone concentrations, results in increased sodium and water retention.
         iii. Increases sex hormone–binding globulin, which is produced in the liver and binds free androgens; this may result in clearing up hormone-mediated acne and unwanted facial hair or hirsutism in women.
      c. Adverse effects attributed to estrogen
         i. Nausea, vomiting
         ii. Bloating, edema
         iii. Irritability
         iv. Cyclic weight gain
         v. Cyclic headache
         vi. Hypertension
         vii. Breast fullness, tenderness
   2. Progestin
      a. Types of progestins available in products in the United States
         i. Norethindrone
         ii. Norethindrone acetate
         iii. Ethynodiol diacetate
         iv. Norgestrel
         v. Levonorgestrel
         vi. Desogestrel
         vii. Norgestimate
         viii. Etonogestrel
         ix. Drospirenone
         x. Dienogest
         xi. Segesterone acetate
      b. Pharmacologic actions of progestins in contraceptives
         i. Feeds back to pituitary and helps inhibit ovulation.
         ii. Causes endometrial atrophy (thinning of uterus lining).
         iii. Thickens cervical mucus (inhibits sperm from traveling).
      c. Adverse effects caused by progestin
         i. Headaches
         ii. Increased appetite
         iii. Increased weight gain
         iv. Depression, fatigue
         v. Changes in libido
         vi. Androgenic adverse effects
            (a) Hair loss, hirsutism
            (b) Acne, oily skin

C. Contraindications for Combined Hormonal Contraceptives
   1. The Centers for Disease Control and Prevention (CDC) medical eligibility criteria are separated into four categories:
      a. A condition for which there is no restriction on the use of contraceptive method (category 1)
      b. A condition in which the advantages of using the method generally outweigh the theoretical or proven risks (category 2)
      c. A condition in which the theoretical or proven risks usually outweigh the advantages of using the method (category 3)
      d. A condition that represents an unacceptable health risk if the contraceptive method is used (category 4)
   2. Category 4 contraindications for combined hormonal contraceptives
      a. Less than 21 days postpartum for women with no risk factors for DVT (regardless of breastfeeding status), 42 days for women with risk factors for DVT (according to CDC recommendations)
      b. Smoker (15 cigarettes or more per day) and/or 35 and older, though conservatively, any smoking can be a risk factor
      c. Several risk factors for CVD
      d. Blood pressure greater than 160/100 mm Hg
      e. Vascular disease
      f. Current DVT or pulmonary embolism or history of DVT or pulmonary embolism
      g. Complicated diabetes showing nephropathy, neuropathy, or retinopathy
      h. Presence of liver tumors, severe cirrhosis, or active viral hepatitis
      i. Major surgery with prolonged immobilization
      j. Known thrombogenic mutations
      k. Current or history of ischemic heart disease
      l. Stroke (history of cerebrovascular accident)
      m. Complicated valvular heart disease
      n. Migraine headache with aura
      o. Current breast cancer
      p. Systemic lupus erythematosus with positive or unknown antiphospholipid antibodies
      q. Complicated solid organ transplantation: Acute or chronic graft failure, rejection, cardiac allograft vasculopathy

D. Adverse Effects (see Estrogen and Progestin sections earlier for specific hormone-causing adverse effects)
   1. According to a 1998 study, discontinuation of contraceptives was attributable to the following:
      a. Bleeding irregularities: 32%
      b. Nausea: 19%
      c. Weight gain: 14%
      d. Mood swings: 14%
      e. Breast tenderness: 11%
      f. Headache: 11%
   2. Management of adverse effects
      a. Breakthrough bleeding
         i. Consider new product after trying the product for 3 months, assess adherence.
         ii. Select new birth control according to when bleeding occurs.
         iii. If early in the cycle, there is probably not enough estrogen; select a regimen with higher estrogen activity.
         iv. If late in the cycle, there is probably not enough progestin; select a regimen with higher progestin activity.
         v. In general, if breakthrough bleeding occurs, it is best to select a regimen with higher estrogen and progestin activities.

b. Nausea
   i. Nausea is more likely to be related to estrogen component.
   ii. Suggest the patient take the pill at night before bed.
   iii. Take the pill with food.
   iv. If possible, try the product for 3 months; nausea may subside.
c. Acne
   i. Acne is more likely to be related to the androgenic properties of progestin.
   ii. Select a product with lower androgenic activity.
   iii. Alternatively, select a product with higher estrogen activity.

3. Serious adverse effects (ACHES)
   a. **A**: Abdominal pain; could signal liver problems or gallbladder.
   b. **C**: Chest pain, shortness of breath, coughing up blood; could signal myocardial infarction or blood clot in lung.
   c. **H**: Headaches (severe); could signal stroke, blood clot.
   d. **E**: Eye problems (blurred vision, flashing lights, blindness); could signal optic neuritis, stroke, clots.
   e. **S**: Severe leg pain with or without swelling; could signal DVT.

Patient Case

6. A 22-year-old woman started taking Lessina 4 months ago for contraception. She has breakthrough bleeding at the start of her active pills that lasts a few days before resolving. The physician wants to change the OC. Which OC on her formulary is best for the physician to prescribe?

Name of OC	Estrogen Property	Progestin Property	Androgen Property
Lessina (levonorgestrel 0.1 mg/ethinyl estradiol 20 mcg)	Low	Low	Low
Reclipsen (desogestrel 0.15 mg/ethinyl estradiol 30 mcg)	Intermediate	High	Low
Necon 0.5/35 (norethindrone 0.5 mg/ethinyl estradiol 35 mcg)	Low	Low	Low
Loestrin (21) 1.5/30 (norethindrone acetate 1.5 mg/ethinyl estradiol 30 mcg)	Low	High	High

A. Continue taking Lessina (levonorgestrel 0.1 mg/ethinyl estradiol 20 mcg) for another 3 months.
B. Change to Reclipsen (desogestrel 0.15 mg/ethinyl estradiol 30 mcg).
C. Change to Loestrin (21) 1.5/30 (norethindrone acetate 1.5 mg/ethinyl estradiol 30 mcg).
D. Change to Necon 0.5/35 (norethindrone 0.5 mg/ethinyl estradiol 35 mcg).

E. Common Drug Interactions (list not all-inclusive)
   1. Increase effect of hormonal contraceptives
      a. Acetaminophen
      b. Ascorbic acid
      c. Atazanavir
      d. Atorvastatin
      e. Ginseng
      f. Indinavir
      g. Red clover (may increase or decrease effect of combined hormonal contraceptives)
      h. Rosuvastatin
      i. Tranexamic acid
      j. Voriconazole

2. Decrease effect of hormonal contraceptives
    a. Amprenavir
    b. Aprepitant
    c. Barbiturates
    d. Bexarotene
    e. Bosentan
    f. Carbamazepine
    g. Darunavir
    h. Efavirenz
    i. Felbamate
    j. Griseofulvin
    k. Lopinavir
    l. Modafinil
    m. Mycophenolate mofetil
    n. Nelfinavir
    o. Nevirapine
    p. Oxcarbazepine
    q. Phenobarbital
    r. Phenytoin/fosphenytoin
    s. Pioglitazone
    t. Primidone
    u. Red clover (may increase or decrease effect of combined hormonal contraceptives)
    v. Rifamycins
    w. Ritonavir
    x. Rufinamide
    y. Saquinavir
    z. St. John's wort
    aa. Tipranavir
3. Drugs that are increased or decreased by hormonal contraceptives
    a. Acetaminophen
    b. Antidepressants, tricyclic
    c. Aspirin
    d. Benzodiazepines
    e. β-Blockers
    f. Caffeine
    g. Clofibric acid
    h. Corticosteroids
    i. Cyclosporine
    j. Fosamprenavir
    k. Lamotrigine
    l. Levothyroxine
    m. Morphine
    n. Paclitaxel
    o. Salicylic acid
    p. Selegiline
    q. Tacrine
    r. Tacrolimus
    s. Theophyllines
    t. Tizanidine
    u. Valproic acid

4. Questionable effects that hormonal contraceptives may have on other drugs
    a. Anticoagulants: Hormonal contraceptives may increase certain clotting factors and reduce antithrombin III, so it is questionable whether hormonal contraceptives interfere with anticoagulants.
    b. Lamotrigine and fosamprenavir concentrations may be decreased by hormonal contraceptives.
5. Simplified list of drug-drug interactions according to the U.S. Medical Eligibility Criteria for Contraceptive Use 2016 (www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6503.pdf)
    a. Nucleoside reverse transcriptase inhibitors, maraviroc, HIV integrase strand transfer inhibitors (category 1: before treating any patients, recommend to check specific product information)
    b. Nonnucleoside reverse transcriptase inhibitors (category 1 or 2: before treating any patients, recommend to check specific product information)
    c. Ritonavir-boosted protease inhibitors (category 2; exception: ritonavir-boosted lopinavir)
    d. Protease inhibitors without ritonavir (category 1: indinavir; category 2: – nelfinavir and atazanavir; category 3: fosamprenavir)
    e. Antiepileptics (category 3)
    f. Rifampin or rifabutin (category 3)
    g. St. John's wort (category 2)
    h. Broad-spectrum antibiotics, antifungals, antiparasitics (category 1); U.S. Medical Eligibility Criteria for Contraceptive Use 2016 suggest that no alternative form of contraception is necessary with broad-spectrum antibiotics, but other antibiotics may require an alternative form of contraception (see text that follows)
    i. Reported antibiotic cases in the literature: Tetracycline, minocycline, erythromycin, penicillins, and cephalosporins; pharmacokinetic studies have not shown decreased OC steroid concentrations with tetracycline, doxycycline, ampicillin, metronidazole, quinolones, or fluconazole.
        i. Proposed mechanisms of drug interactions
            (a) Interference of absorption: Ethinyl estradiol is conjugated in the liver, excreted in bile, hydrolyzed by intestinal bacteria, and reabsorbed as an active drug; non–liver enzyme-inducing antibiotics temporarily decrease colonic bacteria and inhibit enterohepatic circulation of ethinyl estradiol. Gut flora have recovered 3 weeks after the introduction of antibiotics.
            (b) Liver enzyme induction (rifampin and griseofulvin): The metabolism of progesterone and estrogen is accelerated.
        ii. Use a backup method (BUM) for the length of antibiotic therapy plus 7 days after discontinuing antibiotic.

F. Types of Hormonal Contraceptives
    1. Oral
        a. COC regimens
            i. Monophasic: Same amount of hormone in pill every day except in placebo pills
            ii. Biphasic: Amount of hormone may change halfway through cycle.
            iii. Triphasic: Amount of hormone changes every week.
                (a) Traditional: Progestin usually changes and estrogen stays the same.
                (b) Estrophasic: Estrogen changes.
            iv. Quadriphasic: Estrogen changes and progestin changes; four varying amounts throughout monthly pack
        b. Dosing
            i. High-dose estrogen: Higher than 35 mcg (up to 50 mcg)
            ii. Low-dose estrogen: Less than 35 mcg (generally 20–35 mcg)
            iii. Very low-dose estrogen: Less than 10 mcg

c. Effectiveness: When taken every day at the same time, 99.7% (perfect use), typical use (about 93%) (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
d. Adherence: 68% continue after 1 year
e. Start methods
    i. Same-day start: Start taking an active pill the first day of menses.
    ii. Sunday start: Start taking an active pill the first Sunday after menses begins (use a BUM for at least 7 days, most conservative for 1 month).
    iii. Quick start: Start taking an active pill at the physician's office or first day of prescription, regardless of menstrual cycle day. Use a BUM for at least 7 days. Most conservative; use a BUM for 1 month. Menses will not begin until all the active pills have been taken.
    iv. When changing pills from brand to brand, start the new pack of pills after finishing the placebo pills from the old pack.
f. Counseling
    i. Proper use: Take 1 tablet once daily at the same time every day.
    ii. Adverse effects
        (a) See previous text.
        (b) Adverse effects usually subside after 3 months; general recommendation is to stay on a brand for at least 3 months if adverse effects are not excessively bothersome.
    iii. Missed doses: Missed COC pill means more than 24 hours between doses. Recommendations differ on what to do about missed doses.
        (a) Recommendations for missed combined oral contraceptives (MMWR 2016;65 (RR4):1-66)
            (1) Missed 1 pill: Take missed dose as soon as possible, continue taking the remaining doses at the usual time even if it means taking 2 tablets in one day, no BUM needed; generally EC is not necessary but may be considered (except ulipristal) if the patient missed doses earlier in the cycle or in the last week of the previous pack.
            (2) Missed 2 or more pills: If two or more doses are missed, more than 48 hours since scheduled administration time, may recommend the following:
                (A) Take most recent doses as soon as possible.
                (B) Continue taking remaining doses at the usual time even if it means taking 2 tablets in one day.
                (C) Use a BUM or avoid intercourse until 7 active tablets have been taken for 7 consecutive days.
                (D) Use EC (except for ulipristal) if unprotected intercourse occurred in the previous 5 days.
g. Unique formulations (other AB-rated products may be available that are not listed here)
    i. Natazia (estradiol valerate/dienogest), four-phase OC: 2 days, 3 mg of estradiol valerate; 5 days, 2 mg of estradiol valerate/2 mg of dienogest; 17 days, 2 mg of estradiol valerate/3 mg of dienogest; 2 days, 1 mg of estradiol valerate; 2 days, placebo
    ii. Mircette, Azurette, Bekyree, Kariva, Kimidess, Pimtrea, Viorele (ethinyl estradiol/desogestrel): 2 days of placebo and 5 days of estrogen only (10 mcg), instead of 7 days of placebo
    iii. Femcon Fe, Nexesta Fe, Wymzya FE, Zenchent FE (ethinyl estradiol 35 mcg/norethindrone 0.4 mg): Chewable tablets with iron tablets instead of placebo
    iv. Lo Loestrin Fe (ethinyl estradiol 10 mcg/norethindrone acetate 1 mg): Lowest oral estrogen COC tablet; contains 24 active tablets, 2 tablets of ethinyl estradiol 10 mcg, and 2 tablets of ferrous fumarate 75 mg
    v. Generess Fe, Layolis Fe, Kaitlib Fe (ethinyl estradiol 25 mcg/norethindrone 0.8 mg): 24 chewable active tablets and 4 tablets of ferrous fumarate 75 mg

vi. Drospirenone progestin-containing contraceptives
  (a) Drospirenone: Analog of spironolactone, similar to spironolactone 25 mg
  (b) Exercise caution with drugs that increase potassium such as high doses of NSAIDs, heparin, ACE inhibitors, and potassium-sparing diuretics.
  (c) No diuretic effect, has antimineralocorticoid effects, decreases bloating effect of ethinyl estradiol.
  (d) Antiandrogenic: Best for acne, hirsutism, or male pattern balding in women
  (e) Possible increased risk of DVT, FDA safety communication, April 2012
  (f) Products (other AB-rated products may be available)
    (1) Yasmin (ethinyl estradiol 30 mcg/drospirenone 3 mg): 21 active tablets, 7 placebo
    (2) YAZ (ethinyl estradiol 20 mcg/drospirenone 3 mg): 24 active tablets with 4 days of placebo, approved use for premenstrual dysphoric disorder, acne.
    (3) Safyral (ethinyl estradiol 30 mcg/drospirenone 3 mg and 0.451 mg of levomefolate calcium) and 4 tablets of 0.451 mg of levomefolate calcium
    (4) Beyaz: 24 active tablets of ethinyl estradiol 20 mcg, drospirenone 3 mg, and 0.451 mg of levomefolate calcium (folic acid) and 4 tablets of 0.451 mg of levomefolate calcium, approved use for premenstrual dysphoric disorder and acne.

h. Advantages and disadvantages (Table 14)

Table 14. Advantages and Disadvantages of COCs

Advantages	Disadvantages
Effective	No HIV or STI protection
Easy to use	Patient adherence
Reversible	Expensive
Regular menstrual cycle	Adverse effects
Reduction of several cancers	Circulatory complications
Decreased risk of benign breast tumors	Menstrual cycle changes
Improves acne	Sexual and psychological effects
Sexual enjoyment	Hepatocellular adenoma
Emergency contraception	Gallbladder disease
Transition therapy for perimenopause	Drug interactions

COC = combined oral contraceptive (tablet); HIV = human immunodeficiency virus; STI = sexually transmitted infection

2. Transdermal patch (Xulane, Twirla)
  a. Patch placed on skin; Xulane delivers 150 mcg of norelgestromin/35 mcg ethinyl estradiol (provides 60% more estrogen exposure than 35-mcg oral tablet of ethinyl estradiol); Twirla delivers 120 mcg of levonorgestrel/30 mcg of ethinyl estradiol.
  b. Effectiveness
    i. Similar to pills (7% failure rate for typical use, 0.3% for perfect use)
    ii. Less effective in women weighing more than 198 lb (90 kg); should not be used (Twirla is contraindicated if BMI is 30 kg/m^2 or greater)
  c. Adherence: Better adherence rates than pill, especially in teens
  d. Counseling
    i. Proper use
      (a) Place patch on a dry, hairless area of upper arm, shoulder, abdomen, or buttocks. Should not be placed on the breast. Rotate site of patch each week.
      (b) One patch per week for 3 weeks; week 4 is patch free (menses will occur then)

ii. Adverse effects
  (a) Higher incidence of blood clots
  (b) Site irritation from the patch
  (c) See adverse effects mentioned earlier in text.
iii. Missed doses
  (a) If patch is off for less than 24 hours, reapply patch; no BUM needed.
  (b) If patch is off for more than 24 hours, open a new patch, new day 1; must use a BUM for first week of the new cycle.
iv. Alternative recommendations for missed contraceptive patch application (MMWR 2016;65 (RR4):1-66)
  (a) Missed dose = delayed patch application of less than 48 hours or recommended time for application.
    (1) Apply new contraceptive patch as soon as possible (if less than 24 hours, may replace same patch).
    (2) Keep contraceptive patch on until scheduled patch change day.
    (3) No BUM needed
    (4) In general, EC is unnecessary but may be considered (except for ulipristal) if the patient missed doses earlier in the cycle or in the last week of the cycle.
  (b) If delayed application is more than 48 hours from scheduled administration time, may recommend the following:
    (1) Apply new patch as soon as possible.
    (2) Keep patch on until scheduled patch change day.
    (3) Use a BUM or avoid intercourse until contraceptive patch has been in place for 7 consecutive days.
    (4) If doses missed were during days 15–21 of a 28-day cycle (e.g., 3 weeks active hormone, 1 week placebo); then omit the patch-free week and apply a new contraceptive patch.
    (5) If unable to apply a new patch immediately, use a BUM or avoid intercourse until new patch has been applied for 7 consecutive days.
  (c) Use EC (except for ulipristal) if active hormone was missed in the first week of the cycle or unprotected intercourse occurred in the previous 5 days.

e. Advantages and disadvantages (Table 15)

Table 15. Advantages and Disadvantages of Transdermal Contraception Patch

Advantages	Disadvantages
Efficacy Adherence User controlled Readily reversible	Site reactions Patch detachment Appearance, less privacy Breast discomfort Dysmenorrhea Headache Nausea Should not be used in women > 90 kg Questionable increased risk of blood clots

3. Vaginal rings
  a. NuvaRing
    i. Product inserted vaginally; delivers 15 mcg ethinyl estradiol and 120 mcg etonogestrel (active form of desogestrel) daily.

ii. Effectiveness: Similar to pills (7% failure rate for typical use, 0.3% for perfect use) (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
iii. Adherence
  (a) One study found that 92.4% of women using a vaginal ring were adherent versus 75.4% using the COC pill.
  (b) Users were 96% satisfied; 97% would recommend the ring.
  (c) Reasons for liking the ring
    (1) "Not having to remember anything" (45%)
    (2) "Ease of use" (27%) (Contraception 2003;67:187-94)
iv. Counseling
  (a) Proper use
    (1) Insert vaginal ring into vagina and leave for 3 weeks. Week 4, remove ring and menses will occur.
    (2) Should not be removed during intercourse.
    (3) May be worn with tampon if there is breakthrough bleeding.
  (b) Missed doses: Inadvertent removal, expulsion, or prolonged ring-free interval
    (1) If 3 hours or less, rinse with cool to lukewarm water and reinsert as soon as possible.
    (2) If more than 3 hours, reinsert and use a BUM until ring has been used continuously for 7 days.
  (c) Alternative recommendations for missed vaginal ring insertion (MMWR 2016;65(RR4):1-66)
    (1) Missed dose = delayed insertion of less than 48 hours or recommended time for insertion
      (A) Insert new vaginal ring as soon as possible.
      (B) Keep ring in until scheduled ring removal day.
      (C) No BUM needed.
      (D) In general, EC is unnecessary but may be considered (except for ulipristal) if the patient missed doses earlier in the cycle or in the last week of the cycle.
    (2) If delayed insertion is more than 48 hours from scheduled administration time, may recommend the following:
      (A) Insert ring as soon as possible.
      (B) Keep ring in until scheduled ring removal day.
      (C) Use a BUM or avoid intercourse until vaginal ring has been in place for 7 consecutive days.
        • If doses missed were during days 15–21 of a 28-day cycle (e.g., 3 weeks active hormone, 1 week placebo); then omit the ring-free week and insert a new vaginal ring.
        • If unable to insert a new ring immediately, use a BUM or avoid intercourse until new ring has been inserted for 7 consecutive days.
      (D) Use EC (except for ulipristal) if active hormone was missed in the first week of the cycle or unprotected intercourse occurred in the previous 5 days.
  (d) Adverse effects
    (1) Decreased libido (8%)
    (2) Breast tenderness (4%)
    (3) Device-related events (2.5%–5%)
    (4) Vaginal discomfort and secretions (2.5%)
    (5) Irregular bleeding (1.5%–5%)
v. Advantages and disadvantages (Table 16)

b. Annovera
   i. Product inserted vaginally, delivers 0.15 mg/day of segesterone and 13 mcg/day of ethinyl estradiol
   ii. Effectiveness: 96%–98% effective in preventing pregnancy, has not been studied in women with a BMI greater than 29 kg/m^2
   iii. Counseling:
      (a) Proper use
         (1) Insert vaginal ring into vagina and leave for 3 weeks. Week 4, remove ring and menses will occur
         (2) Should not be removed during intercourse
      (b) Missed doses:
         (1) If out 2 hours or less, rinse with warm water and reinsert as soon as possible
         (2) If out 2 hours or more at one time or out for a time that adds up to more than 2 hours over the 21 days, a backup contraceptive method should be used until the ring has been in place continuously for 7 days
      (c) Adverse effects (greater than 5%)
         (1) Headache/migraine
         (2) Nausea/vomiting/diarrhea
         (3) Abdominal pain
         (4) Yeast infections
         (5) Dysmenorrhea
         (6) Vaginal discharge
         (7) Breast tenderness
         (8) Menstrual irregularities
         (9) Urinary tract infections
         (10) Genital itching
      (d) Drug interactions
         (1) Similar to those with combined hormonal contraceptives
         (2) Increased exposure to hormones occurs with oil-based suppositories such as miconazole 1- or 3-day treatments. Only water-based suppositories should be used concurrently with this vaginal ring.
      (e) Contraindications – Similar to combined hormonal contraceptives

Table 16. Advantages and Disadvantages of Contraceptive Vaginal Ring

Advantages	Disadvantages
Efficacy Adherence User controlled Cycle control Readily reversible Privacy	Adverse effects similar to other combined regimens Vaginal discomfort Potential partner awareness of ring

4. Extended regimens (other AB-rated products may be available that are not listed here)
   a. 3 months: Using active form of combined hormonal contraception for 3 months (results in menses every 3 months instead of once a month)
      i. Ethinyl estradiol 30 mcg/levonorgestrel 150 mcg, ethinyl estradiol 10-mcg tablets instead of placebo pills (Seasonique, Amethia, Ashlyna, Daysee, Camrese)

ii. Ethinyl estradiol 20 mcg/levonorgestrel 100 mcg, ethinyl estradiol 10-mcg tablets instead of placebo pills (LoSeasonique, Amethia Lo, Camrese Lo)
iii. 42 tablets of ethinyl estradiol 20 mcg and levonorgestrel 0.15 mg, 21 tablets of ethinyl estradiol 20 mcg and levonorgestrel 0.15 mg, 21 tablets of ethinyl estradiol 30 mcg and levonorgestrel 0.15 mg, and 7 tablets of ethinyl estradiol 10 mcg instead of placebo pills (Quartette)
iv. 84 tablets levonorgestrel 0.15 mg and ethinyl estradiol 30 mcg (Jolessa, Quasense, Introvale)

b. 1 year: Using active form of combined hormonal contraception for 1 year; product: ethinyl estradiol 20 mcg/levonorgestrel 90 mcg (Amethyst)

VIII. PROGESTIN-ONLY CONTRACEPTIVES, CONTAINING ONLY A PROGESTIN AGENT WITH NO ESTROGEN

A. Indications: Those who cannot use or tolerate combined hormonal contraceptives (see list that follows) or those seeking long-term contraception
1. History of or current MI, stroke, DVT, CVD
2. Atrial fibrillation
3. Blood pressure 160/100 mm Hg
4. Smoker age 35 or older
5. Active, symptomatic liver disease
6. Benign or malignant liver tumors
7. History of cholestasis because of estrogen-containing products
8. Migraine headache with neurologic impairment or aura
9. Retinopathy or neuropathy because of diabetes
10. Surgery within the past 4 weeks
11. Breastfeeding

B. Components: One of the following progestins
1. Norethindrone 0.35 mg (Micronor, Nor-QD, Camila, Errin, Jolivette, Nora-BE, Deblitane, Heather, Lyza, Jencycla, Norlyroc, Sharobel)
2. Drospirenone 4 mg (Slynd)
3. Depot medroxyprogesterone acetate (DMPA [Depo-Provera injectable/Depo-Provera subcutaneously])

C. Mechanisms of Action
1. Thickens cervical mucus, prevents sperm movement.
2. Thins uterus lining.
3. Suppresses midcycle peak of LH and FSH, inhibits ovulation (minimal with oral progestin pills).

D. Contraindications
1. Suspected or demonstrated pregnancy
2. Active hepatitis, hepatic failure, jaundice
3. Inability to absorb sex steroids from GI tract (i.e., active colitis)
4. Concurrently taking medications that increase hepatic clearance (CYP inducers). Note: Medroxyprogesterone acetate okay to use with CYP inducers.
5. Taking an antibiotic such as rifampin or rifabutin (category 3), broad-spectrum antibiotics (category 1).

E. Adverse Effects: See progestin adverse effects in Combined Hormonal Contraceptives section mentioned earlier in text.

F. Types
   1. Oral
      a. Norethindrone 0.35 mg (Camila, Deblitane, Errin, Heather, Jencycla, Jolivette, Lyza, Nora-BE, Norlyroc, Nor-QD, Micronor, Sharobel) - aka traditional mini-pill
         i. Effectiveness: 7% failure rate (typical), 0.3% failure (perfect use) (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
         ii. Start methods: May start on any day or on first day of period. There are no hormone-free days with the POPs.
         iii. Adverse effects: Progestin related (see earlier text)
         iv. Missed doses: Doses of POPs must be at the SAME time every day; a missed dose of POPs means more than 3 hours. If a missed dose occurs, must use a BUM for 48 hours.
         v. Advantages
            (a) Efficacy
            (b) Decreased menstrual blood loss, cramps, pain
            (c) Readily reversible
            (d) Preferable in lactating women
         vi. Disadvantages
            (a) Progestin-related adverse effects (e.g., weight gain, acne)
            (b) Irregular menses
            (c) Adherence: Short time window for a missed pill
            (d) Low-dose progestin; patient may ovulate
            (e) Fewer noncontraceptive benefits
      b. Drospirenone 4 mg (Slynd)
         i. Effectiveness: 98% effective in preventing pregnancy
         ii. Start methods: Start active tablet on the first day of menses. There are 24 active tablets and 4 inactive tablets.
         iii. Adverse effects: Acne, metrorrhagia, headache, breast pain or tenderness, weight gain, dysmenorrhea, nausea, vaginal hemorrhage, decreased libido, and irregular bleeding
         iv. Missed doses: If 1 active tablet is missed, take as soon as possible and finish the pill pack as instructed. If 2 active tablets are missed, take the last missed tablet as soon as possible. Continue taking 1 tablet a day as instructed. Use an additional BUM for 7 days.
         v. Advantages: Dosing is not as sensitive to timing as for traditional POPs.
         vi. Disadvantages
            (a) Progestin-related adverse effects
            (b) Irregular menses
            (c) Monitoring of thromboembolism, hyperkalemia, bone loss
   2. Depot medroxyprogesterone acetate (DMPA) Depo-Provera injection
      a. A 1-mL crystalline suspension of 150 mg of DMPA injected intramuscularly into deltoid or gluteus maximus muscle every 11–13 weeks
      b. Effectiveness: Perfect use failure rate: 0.3%; typical use failure rate: 4% (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
      c. Start methods
         i. Preferred start: First 5 days of menses. No BUM needed.
         ii. Alternative start: Any time in cycle if not pregnant. Use BUM for 7 days.
         iii. Postpartum: May give injection before hospital discharge.
         iv. Breastfeeding: May start immediately or wait 4–6 weeks.
         v. Switching methods: Any time patient not known to be pregnant. Use BUM if necessary.

d. Adverse effects
   i. Progestin related (see earlier text)
   ii. Progressive significant weight gain
   iii. Severe depression (rare)
   iv. Boxed warning: Loss of bone; women who used DMPA for at least 5 years have significantly reduced BMD of lumbar spine and femoral neck, particularly after 15 years of use and if initiated before age 20.
      (a) The effect is almost completely reversible, even after 4 years or more of DMPA use.
      (b) All women placed on DMPA should be taking sufficient calcium and exercising regularly.
e. Missed dose: More than 13 weeks between injections
f. Patient counseling
   i. Wait a few hours before massaging area where shot was given.
   ii. Irregular bleeding or spotting in the beginning which will decrease over time.
   iii. Take calcium if not achieving 1000–1200 mg/day through diet.
   iv. Return in 11–13 weeks for next injection. Use BUM if ever more than 13 weeks.
   v. If ever changing from DMPA to another method, start method when next injection is due.
   vi. May have delayed return to fertility for up to 18 months. Use with caution in women 35 years or older who express interest in future conception.

3. Depo-Provera subcutaneously: Subcutaneous injection of 104 mg DMPA, information similar to that stated earlier but, in addition, has FDA indication for endometriosis.

IX. INTRAUTERINE DEVICES (IUDs) AND SYSTEMS (IUSs)

A. Indications: To prevent pregnancy long term; levonorgestrel IUS is also indicated for heavy menses in women who elect to use an IUD for contraception.

B. Recommended for Women Who:
   1. Have no history of pelvic inflammatory disease (PID) or ectopic pregnancy
   2. Have heavy menses, cramps, anemia, or dysfunctional uterine bleeding (Mirena only)
   3. Are seeking long-term (2 years or more) pregnancy protection
   4. Do not want to use estrogen-containing products

C. Types
   1. Copper (ParaGard T 380A)
      a. Copper IUD inserted into the uterus by a health care professional
      b. Mechanism of action
         i. Primary action: Spermicidal
         ii. Copper ions inhibit sperm motility and acrosomal enzyme activation so that sperm seldom reach fallopian tube and are unable to fertilize the ovum.
         iii. A sterile inflammatory reaction created in endometrium phagocytizes sperm.
         iv. Does not interfere with ovulation and is not an abortifacient.
      c. Effectiveness: Perfect use failure rate: 0.6%; typical use failure rate: 0.8% (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
      d. Contraindications specific to copper IUD
         i. Pregnancy
         ii. Women with current or recent (within 3 months) sexually transmitted infection (STI) or woman at risk of STI

iii. Uterus less than 6 cm or greater than 9 cm
iv. Undiagnosed abnormal vaginal bleeding
v. Active cervicitis or active pelvic infection
vi. Known symptomatic actinomycosis
vii. Recent endometritis (past 3 months)
viii. Allergy to copper; Wilson's disease
ix. Uterine distortion or pathology affecting placement
x. Known or suspected uterine or cervical cancer
xi. Unresolved abnormal Papanicolaou (Pap) test
xii. Severe anemia (relative contraindication)

e. Advantages and disadvantages (Table 17)

Table 17. Advantages and Disadvantages of Copper IUD

Advantages	Disadvantages
Efficacy (long term, 10 yr)	Monthly blood loss increased about 35%
Adherence	Dysmenorrhea
Spontaneous sexual activity	Spotting and cramping
Readily reversible	Expulsion
Cost-effective	Foreign body
Patient satisfaction	Increased risk of infection for 20 days after insertion

IUD = intrauterine device

2. Progestin (levonorgestrel; Kyleena, Mirena, Liletta, Skyla)
   a. Kyleena: Inserted into uterus by health care professional, stays in for up to 5 years, releases 17.5 mcg levonorgestrel per day, indicated for contraception.
   b. Liletta: Inserted into uterus by a health care professional; stays in for up to 5 years; releases 18.6 mcg/day initially and declines steadily to 16.3 mcg/day at 1 year, 14.3 mcg/day at 2 years, and 12.6 mcg/day at 3 years; indicated for contraception.
   c. Mirena: Inserted into uterus by health care professional, stays in for up to 6 years, releases 20 mcg levonorgestrel per day, indicated for contraception and menorrhagia.
   d. Skyla: Inserted into uterus by a health care professional; stays in for up to 3 years; releases 14 mcg levonorgestrel per day after 24 days, decreasing to 10 mcg/day after 60 days and then to less than 5 mcg after 3 years; indicated for contraception.
   e. Mechanism of action
      i. Foreign object in uterus, prevents implantation
      ii. Progestin thickens cervical mucus, thins endometrium, and inhibits sperm motion.
      iii. Effectiveness: 99% effective in preventing pregnancy
   f. Contraindications (package insert)
      i. Pregnancy or suspicion of pregnancy
      ii. Congenital or acquired uterine anomaly
      iii. Acute or history of PID
      iv. Postpartum endometritis or infected abortion in the past 3 months
      v. Known or suspected uterine or cervical neoplasia
      vi. Unresolved abnormal Papanicolaou (Pap) test
      vii. Genital bleeding of unknown etiology
      viii. Untreated acute cervicitis or vaginitis
      ix. Acute liver disease or liver tumor (benign or malignant)
      x. Woman or partner with several sexual partners

xi. Conditions associated with increased susceptibility to infections with microorganisms (e.g., leukemia, acquired immunodeficiency syndrome, intravenous drug abuse)
xii. Genital actinomycosis
xiii. A previously inserted IUD that has not been removed
xiv. Hypersensitivity to any component of this product
xv. Known or suspected carcinoma of the breast
xvi. History of ectopic pregnancy or condition that would predispose to ectopic pregnancy

g. Advantages and disadvantages (Table 18)

Table 18. Advantages and Disadvantages of Progestin IUS

Advantages	Disadvantages
Efficacy (long term, 3–6 yr) Adherence Menorrhagia improves Spontaneous sexual activity Readily reversible	Progestin-related adverse effects Irregular menses (generally for the first 6 mo; then possibly amenorrhea) Expulsion Increased risk of infection first 20 days after insertion Foreign body

IUS = intrauterine system

D. Contraceptive CHOICE Project (Clin Obstet Gynecol 2014;5:635-43; and N Engl J Med 2014;371:1316-23)
1. Enrolled over 9000 women and girls, 14–45 years of age, not planning to conceive in the next 12 months; sexually active (or planning) with male partner; willing to start a new contraceptive method; enrolled in a study in St. Louis
2. Study looked at the use of long-acting reversible contraception (LARC) that included IUDs and implants, followed for 3 years.
3. Women were provided contraceptive of choice at no cost. Women had the choice of pill, patch, vaginal ring, levonorgestrel IUD, copper IUD, or progestin implant.
4. Findings
   a. LARC methods chosen by 75% of women
   b. Continuation rates for LARC (implants and IUDs) were higher than for short-acting methods (86% vs. 55% at 12 months and 77% vs. 41% at 24 months).
   c. Sexual behaviors did not change; 71% of participants reported no change in partners at 6 and 12 months.
   d. Failure rates for pill, patch, and ring users were higher (4.8%–9.4%) than for LARC users (less than 1%) over the 3 years.
   e. Those who used shorter-acting birth control methods compared with LARC were 22 times more likely to have an unintended pregnancy.
   f. Showed safety of LARC use among teens (15–19 years of age).

E. Patient Counseling
1. Strings of IUD will be outside the vaginal canal. Patient will be instructed on how and when to check the strings to verify IUD is still inserted correctly.
2. Adverse effects: PAINS
   a. **P:** Period late; abnormal spotting or bleeding
   b. **A:** Abdominal pain, pain with intercourse
   c. **I:** Infection exposure (STI); abnormal vaginal discharge
   d. **N:** Not feeling well, fever, chills
   e. **S:** String missing, shorter, or longer

Patient Case

7. L.M., a 37-year-old woman (height 67 inches, weight 95 kg), states that she is getting married soon and wants to begin contraception for now; however, she would like to have children in a year or so. Her medical history includes hypertension for 2 years and gastroesophageal reflux disease; she drinks 2 glasses of wine a week and smokes ½ pack of cigarettes/day. Her medications include hydrochlorothiazide 25 mg orally daily,amlodipine 5 mg /benazepril 20 mg (Lotrel 5/20) orally daily,omeprazole 20 mg orally daily, and occasional ibuprofen. Which contraceptive product is best to recommend for L.M.?
   A. Transdermal contraceptive patch
   B. Oral tablet ethinyl estradiol/drospirenone
   C. Oral tablet norethindrone
   D. DMPA IM injection

X. IMPLANT (NEXPLANON)

A. Indication: Long-term prevention of pregnancy

B. Components: Etonogestrel, releases 60–70 mcg/day during weeks 5–6 and then decreases to 35–45 mcg/day by the end of the first year, 30–40 mcg/day after the second year, and 25–30 mcg/day at the end of 3 years. Of note: etonogestrel (Implanon) has been discontinued; only etonogestrel (Nexplanon) is being manufactured and distributed currently.

C. Mechanism of Action: A rod inserted in upper arm, 99% effective for up to 3 years, releases progestin etonogestrel, which acts similarly to other progestin-only contraceptives; not tested in women weighing more than 130% of their ideal body weight; may be less effective in overweight women; return to fertility within 1–3 months; Nexplanon is radio-opaque so it is visible on radiograph.

D. Adverse Effects
   1. Similar to progestin-related adverse effects.
   2. Bleeding irregularities
   3. Site reactions, inflammation, hematoma, pain, redness at site (3.6%)
   4. Difficulty removing rod after 3 years, rod breaks, fibrosis (1.7%)

E. Studies (see Contraceptive CHOICE Project under IUD section)

XI. EMERGENCY CONTRACEPTION

A. Definition: "A therapy used to prevent pregnancy after an unprotected or inadequately protected act of sexual intercourse." ACOG definition (ACOG Practice Bulletin 152. Obstet Gynecol 2015;126(3):e1-11.)

B. Mechanism of Hormonal Methods (Yuzpe and progestin-only)
   1. Inhibits ovulation
   2. Prevents fertilization
   3. Increases thickness of cervical mucus
   4. Prevents implantation (controversial; most recent data suggest this does not occur)
   5. Not considered an abortifacient by medical standards; does not disrupt an implanted, fertilized egg.

C. Indications
   1. Condom broke
   2. Misused contraceptive method (e.g., missed a pill, contraceptive patch fell off)
   3. Sexual assault
   4. Exposure to teratogen
   5. Unprotected intercourse within 120 hours

D. Timing: Within 120 hours after unprotected intercourse; package insert for marketed products (levonorgestrel products) states 72 hours, but studies show up to 120 hours may still prevent pregnancy.

E. Effectiveness: 57%–85%

F. Methods
   1. Yuzpe method (not frequently utilized clinically)
      a. High-dose estrogen plus progestin
      b. FDA labeling-approved doses (based on norgestrel or levonorgestrel)
         i. Ethinyl estradiol 50 mcg/norgestrel 0.5 mg (Ogestrel 0.5/50): 2 tablets immediately, then 2 tablets 12 hours later
         ii. Ethinyl estradiol 30 mcg/norgestrel 0.3 mg (Low-Ogestrel, Cryselle, Elinest): 4 tablets immediately, then 4 tablets 12 hours later
         iii. Ethinyl estradiol 30 mcg/levonorgestrel 0.15 mg (e.g., Altavera, Ayuna, Chateal EQ, Lillow, Quasense, Setlakin, Chateal, Kurvelo, Levora, Marlissa, Portia, Jolessa, Introvale) : 4 tablets immediately, then 4 tablets 12 hours later
         iv. Ethinyl estradiol 30 mcg/levonorgestrel 0.125 mg (e.g., Trivora, yellow tablets only): 4 tablets immediately, then 4 tablets 12 hours later
         v. Ethinyl estradiol 20 mcg/levonorgestrel 0.1 mg (e.g., Afirmelle, Aubra, Aubra EQ, Delyla, Larissia, Vienva Falmina, Orsythia, Sronyx, Lessina, Lutera, Aviane): 5 tablets immediately, then 5 tablets 12 hours later
      c. Adverse effects
         i. Nausea: 30%–60%; vomiting: 33% with estrogen-containing EC (if vomiting within 2 hours of dose, repeat dose; may take with food or meclizine 50 mg prophylactically 30–60 minutes before each dose)
         ii. May notice changes in menstrual cycle
         iii. Breast tenderness, headache
   2. Progestin-only method
      a. Products: Levonorgestrel 1.5 mg, 1 tablet (Plan B One-Step, Next Choice One Dose, New Day, My Way, Take Action, Aftera, EContra EZ, EContra One-Step, Fallback Solo, Opcicon One-Step, React)
         i. Available over the counter (OTC) for use by women; men or women may purchase.
         ii. Available OTC for all ages
      b. Adverse effects
         i. Nausea: 18%; vomiting: 4%
         ii. May notice changes in menstrual cycle
         iii. The WHO recommends using levonorgestrel only. A double-blind, randomized study of 2000 women showed that levonorgestrel 750 mcg repeated 12 hours later prevented 85% of pregnancies versus the Yuzpe regimen (ethinyl estradiol 100 mcg/levonorgestrel 0.5 mg repeated 12 hours later), which prevented 57%. Less nausea and vomiting occurred with levonorgestrel 750 mcg (Lancet 1998;352:428-33).

c. Special populations
   i. BMI greater than 25 kg/m^2
      (a) Progestin-only emergency contraceptive pills are not as effective for those with a BMI of 25 kg/m^2 or greater. Either ulipristal acetate (ella) or the copper IUD (Paragard T380A) is recommended for these patients. CDC Medical Eligibility criteria state that hormonal methods of EC may lose effectiveness at a BMI of 30 kg/m^2 and higher.
      (b) Controversial: FDA asking for more data and not recommending package labeling changes for levonorgestrel at this time for increased BMI and decreased effectiveness (www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109775.htm)
      (c) The copper IUD is recommended for those with a BMI greater than 35 kg/m^2.
   ii. Weight
      (a) Some studies state levonorgestrel is less effective in women who weigh more than 75 kg and not effective in women who weigh more than 80 kg.
      (b) Controversial: European Medicines Association disagrees, stating that data are lacking and weight does not determine effectiveness of levonorgestrel.
   iii. Breastfeeding women: All EC methods are category 1 for use according to the CDC Medical Eligibility Criteria; exception: breastfeeding not recommended within 24 hours of taking ulipristal because of high concentrations of ulipristal in milk during first 24 hours, with the highest peak 1–3 hours after administration (breast milk for first 24 hours after administration should be discarded)

3. Ella (ulipristal acetate)
   a. Prescription only
   b. Progesterone receptor modulator: Binds to progesterone receptor
   c. Indicated for EC within 120 hours of unprotected intercourse; reported to have 42% more effectiveness in preventing pregnancy than levonorgestrel at 72 hours postcoitus
   d. Dose = 30 mg orally within 120 hours of unprotected intercourse
   e. Adverse effects: Headache, nausea, abdominal pain, dysmenorrhea, menstrual changes
   f. Not approved for use during breastfeeding
   g. Not recommended for women with a BMI greater than 35 kg/m^2, category 2 for women with a BMI of greater than 30 kg/m^2; copper IUD is recommended instead
   h. Use BUM for 7 days after taking ulipristal if using hormonal contraception because ulipristal blocks progesterone receptors.
   i. Recommended to wait 5 days before initiating or resuming hormonal contraception after taking ulipristal. Starting hormonal contraception before waiting 5 days might alter the effect of ulipristal as well as the effect of hormonal contraception.
4. Copper IUD: May be used within 5 days of unprotected intercourse; requires in-office visit.
5. RU-486: May be used within 5 days of unprotected intercourse but will disrupt an established pregnancy; requires in-office visit.

XII. MENSTRUAL DISORDERS (Independent Study)

A. Amenorrhea
   1. Definitions
      a. Primary: Absence of menarche by age 16 years with presence of secondary development or age 14 years with absence of secondary development and absence of menarche
      b. Secondary: Absence of menses for 6 months or three cycles (more common than primary)

2. Causes
    a. Rule out pregnancy.
    b. Excessive exercise or low BMI
    c. Hyperprolactinemia
    d. Polycystic ovary syndrome (PCOS)
    e. Unknown
3. Treatment
    a. Excessive exercise or low BMI
        i. Decrease exercise and encourage weight gain.
        ii. Combined hormonal contraceptives
        iii. Estrogen therapy
            (a) Conjugated estrogens 0.625 to 1.25 mg orally daily on cycle days 1–25
            (b) Transdermal estrogen patch, ethinyl estradiol 50 mcg/day patch
    b. Hyperprolactinemia
        i. Bromocriptine 2.5 mg orally daily
        ii. Cabergoline 0.25 mg orally twice weekly; then increase as needed.
    c. PCOS (see Endocrine and Metabolic Disorders chapter)
    d. Unknown primary
        i. Combined hormonal contraceptives
        ii. Estrogen therapy
            (a) Conjugated estrogens 0.625 to 1.25 mg orally daily on cycle days 1–25
            (b) Transdermal estrogen patch, ethinyl estradiol 50 mcg/day patch
    e. Unknown secondary
        i. Progestins
            (a) Micronized progesterone 400 mg orally daily for 10 sequential days to induce menses
            (b) Medroxyprogesterone acetate 5 to 10 mg orally daily on days 14–25 to induce menses
        ii. Combined hormonal contraceptives

B. Abnormal Uterine Bleeding
    1. Definition: "Bleeding from the uterine corpus that is abnormal in regularity, volume, frequency or duration in the absence of pregnancy." ACOG Committee Opinion No. 557 April 2013
    2. Causes
        a. Structural: "PALM"
            i. **P**olyp
            ii. **A**denomyosis
            iii. **L**eiomyoma
            iv. **M**alignancy and hyperplasia
        b. Nonstructural: "COEIN"
            i. **C**oagulopathy
            ii. **O**vulatory dysfunction
            iii. **E**ndometrial
            iv. **I**atrogenic
            v. **N**ot yet classified
    3. Assessment
        a. Initial laboratory testing
            i. Complete blood cell count
            ii. Blood type and cross-match
            iii. Pregnancy test

b. Check for disorders of hemostasis
    i. PTT, PT, aPTT
    ii. Fibrinogen
    iii. Markers for von Willebrand disease
c. Other laboratory tests
    i. Thyroid-stimulating hormone
    ii. Iron concentrations
    iii. Liver function tests
    iv. *Chlamydia trachomatis*

4. Treatment: Goal is to control current episode of heavy bleeding and reduce menstrual loss in subsequent cycles.
    a. Acute
        i. Hormonal therapy: First line
            (a) Progestins: Medroxyprogesterone acetate 20 mg orally three times daily for 7 days (for acute bleeding)
            (b) Estrogens: Intravenous conjugated equine estrogens
            (c) Combined hormonal contraceptives: Best if at least 35 mcg of ethinyl estradiol and monophasic; Estradiol valerate and dienogest (Natazia) has approved indication for heavy menstrual bleeding.
        ii. Tranexamic acid
        iii. Desmopressin (use with caution; may help for those with von Willebrand disease)
        iv. Surgery
            (a) Hysterectomy
            (b) Endometrial ablation (not recommended as primary therapy)
    b. Chronic
        i. Hormonal therapy: First line
            (a) Progestins
                (1) Medroxyprogesterone acetate 5–10 mg orally for 5–10 days starting on day 16 or day 21 of a 28-day cycle
                (2) Levonorgestrel IUD
            (b) Combined hormonal contraceptives: Low dose may be option.
        ii. Surgery
            (a) Hysterectomy
            (b) Endometrial ablation (not recommended as primary therapy)

C. Dysmenorrhea
1. Definition: Painful menses, usually cramping right before or during menses
2. Causes
    a. Primary: Caused by menstrual period, mediated by prostaglandins
    b. Secondary: Caused by disorder in reproductive system (endometriosis, fibroids, adenomyosis), usually starts later in life.
3. Treatment
    a. NSAIDs: Begin 1–2 days before menses
    b. Heating pad (topical heat)
    c. Hormonal contraceptives: Combined hormonal contraceptives or levonorgestrel IUD

D. Endometriosis
   1. Definition: Chronic disorder that may result in chronic pain and infertility, endometrial tissue found outside the uterus
   2. Treatment
      a. Hormonal contraceptives
         i. Combined hormonal contraceptives (not FDA-approved use)
         ii. Depot medroxyprogesterone acetate (subcutaneous formulation, FDA-approved use)
         iii. Levonorgestrel IUS (not FDA-approved use)
      b. Gonadotropin-releasing hormone (GnRH) agonists: Goserelin, leuprolide, nafarelin, triptorelin
         i. Consider adverse effects such as osteopenia, hot flashes, vaginal dryness.
         ii. Recommend calcium 1000 mg orally daily while taking GnRH agonist.
         iii. May use add-back therapy with norethindrone with or without low-dose conjugated estrogen; transdermal patch with estradiol and medroxyprogesterone acetate may also be used if norethindrone is not well tolerated.
         iv. See GnRH analog drug information in the Infertility section that follows.
      c. GnRH antagonists: Elagolix (Orilissa) - Approved for the treatment of moderate to severe pain associated with endometriosis and endometriosis with dyspareunia (NEJM 2017;377:28-40)
         i. Endometriosis dose - 150 mg orally once daily, maximum use 24 months
         ii. Endometriosis with dyspareunia - 200 mg orally twice daily, maximum use 6 months
         iii. For moderate hepatic impairment, the dose is 150 mg orally once daily for a maximum of 6 months.
         iv. Adverse effects: Bone loss, mood changes, elevated liver function enzymes
         v. Contraindications: Pregnancy, severe osteoporosis, severe hepatic impairment, use of strong organic anion transporting polypeptide 1B1 inhibitors; may decrease effect of estrogen-containing contraceptives (best to use non-hormonal method of contraception during treatment as well as for 7 days after treatment with elagolix)
      d. Danazol
         i. Androgenic agent
         ii. Adverse effects: Acne, hirsutism, myalgias
      e. Aromatase inhibitors: Anastrozole or letrozole, need hormonal contraceptive in addition to minimize risk of ovarian stimulation.
      f. NSAIDs
         i. Used to help decrease pain
         ii. Ibuprofen and naproxen
      g. Surgery

E. PCOS (see Chapter, "Endocrine and Metabolic Disorders")

XIII. INFERTILITY

A. Background
   1. Using no birth control method, women have an 85% chance of pregnancy over 1 year.
   2. About 20% of women have their first baby after age 35.
   3. Probability of having a baby decreases 3%–5% every year after age 30; faster after age 40.
   4. Miscarriages: 12%–15% for those in their 20s, 50% after age 40

B. Things That Can Increase Fertility
   1. Diet
      a. Protein, fruits, and vegetables
      b. Men need zinc.
   2. Exercise, although too much may stop ovulation.
   3. Fertility improves with BMI of 20–25 kg/m^2 or within 15% of ideal body weight; fertility decreased in those less than 95% of ideal body weight or in those greater than 125% of ideal body weight.

C. Definition
   1. Couples who have had unprotected intercourse for 1 year who have not conceived
   2. Couples in which the woman is 35 years or older, the couple is having unprotected intercourse, and the couple has not conceived within 6 months

D. Risk Factors
   1. Age older than 35 years
   2. Tobacco use
   3. Alcohol use
   4. Caffeine use (more than 500 mg/day)
   5. Vitamin D deficiency
   6. Excessive exercise
   7. BMI less than 19 kg/m^2 or more than 25 kg/m^2 for women

E. Causes of Infertility
   1. Male factor
      a. Endocrine: Spermatogenesis, hypogonadism
      b. Anatomic: Blockage, abnormal anatomy
      c. Sexual dysfunction: Ejaculation or erection difficulties
   2. Female factor
      a. Ovulatory
         i. WHO group I: Hypogonadotropic hypogonadal anovulation
            (a) About 5%–10% of anovulatory women
            (b) Low estrogen, low FSH
         ii. WHO group II: Eugonadotropic anovulation (normogonadotropic normoestrogenic anovulation)
            (a) About 75%–85% of anovulatory women
            (b) Normal FSH concentrations
            (c) Women with PCOS generally fall into this classification.
         iii. WHO group III: Hypergonadotropic anovulation
            (a) About 10%–20% of anovulatory women
            (b) Elevated FSH concentrations
            (c) Premature ovarian failure or advanced age fall into this classification.
         iv. Hyperprolactinemic anovulation
            (a) About 5%–10% of anovulatory women
            (b) May have hyperprolactinemia.
            (c) Laboratory values may appear similar to those in WHO group I.
      b. Cervical
         i. Abnormality
         ii. Blockage
         iii. Thickened cervical mucus

c. Pelvic
    i. Fibroids
    ii. Endometriosis
    iii. Fallopian tube damage or blockage
    iv. Uterine abnormality
    v. Pelvic adhesions

F. Medical Conditions in Women
1. PCOS
2. Endometriosis
3. Pelvic inflammatory disease
4. Uterine fibroids
5. Idiopathic

G. Fertility Agents
1. Clomiphene citrate
    a. Brand names: Clomid (discontinued but original brand name), Serophene
    b. Used to stimulate or induce ovulation (used off-label to increase sperm production in men)
    c. Administered for 5 days starting on days 2, 3, 4, or 5 of cycle
    d. Taken by mouth usually 50–150 mg/day
    e. First-line agent
    f. Selective estrogen receptor modulator that works by blocking estrogen receptors; body perceives hypoestrogenic state and increases the release of GnRH, which increases concentrations of FSH and LH.
    g. Adverse effects: Hot flashes, abdominal and breast tenderness, mood swings, visual alterations
2. Aromatase inhibitors (off-label use)
    a. Brand names: Femara (letrozole), Arimidex (anastrozole)
    b. Increase GnRH and gonadotropins
    c. Help induce ovulation with less risk of multiple follicles stimulated (less risk of multiple births).
    d. Adverse effects: Headache, GI complaints, joint pain, bone pain, edema, sweating, and flushing
3. Human menopausal gonadotropin (hMG)
    a. Brand names: Menopur
    b. Class known as menotropins, both FSH and LH
    c. Derived from the urine of postmenopausal women
    d. Pergoveris (recombinant FSH and recombinant LH): Not yet available in the United States
    e. Given on day 2 or 3 of cycle and continued for 7–10 days, or as determined by estradiol concentrations and ultrasound monitoring of follicle development.
    f. Regimens may vary for in vitro protocols.
    g. Adverse effects: Flu-like symptoms, muscle aches, malaise, headaches, dizziness, pain at site
4. Follicle-stimulating hormone (FSH)
    a. Naturally occurring (urine source): Bravelle urofollitropin(Bravelle)
    b. Recombinant: follitropin alpha (Gonal-f), follitropin beta(Follistim)
    c. Injection form
    d. Highly purified
    e. Helps stimulate development of follicle in ovary; given in the first half of the cycle.
    f. Adverse effects: Mood swings, depression, breast tenderness and swelling, pain at site

5. Human chorionic gonadotropin (hCG)
    a. Recombinant: Ovidrel injection subcutaneously
    b. Naturally occurring: Derived from urine of pregnant women, Pregnyl or Novarel, injection intramuscularly
    c. Similar to LH.
    d. Helps stimulate release of egg; given 36 hours before insemination or harvest.
    e. Adverse effects: Irritation at site of injection, edema, headache, mood changes, thromboembolic disorder, allergic reactions
6. GnRH analogs
    a. Used to prevent LH surge that occurs right before ovulation, which helps with timing of ovulation.
    b. Helps optimize the effectiveness of hMG or FSH.
    c. Administered by nasal spray, injection, or capsule
    d. Also used to treat endometriosis.
    e. Induces "menopause" state; may cause osteoporosis in women who use agents for long periods; not usually the case in infertility treatment, but more so for endometriosis.
    f. Agonists versus antagonists
        i. GnRH agonists
            (a) Leuprolide (Lupron), nafarelin (Synarel)
            (b) Adverse effects: Hot flashes, headache, mood swings, insomnia, vaginal dryness, decreased breast size, bone loss
        ii. GnRH antagonists
            (a) Ganirelix and cetrorelix (Cetrotide)
            (b) More recently investigated for infertility protocols versus traditional use of GnRH agonists.
            (c) Said to have fewer complications.
            (d) Faster onset of action than agonists
7. Metformin
    a. Sometimes used in conjunction with clomiphene to help ovulation in women with PCOS.
    b. Increases insulin sensitivity and decreases hyperinsulinemia, thus reducing circulating androgens.
    c. Weight loss may also occur, leading to better outcomes for ovulation.

H. Other Fertility Agents
1. Progesterone: Used for luteal phase support or for patients with frequent miscarriages
    a. Capsules (micronized): Orally, vaginally
    b. Injectables
    c. Vaginal suppositories
2. Bromocriptine: Decreases prolactin concentrations; prolactin lowers progesterone concentrations, may prevent ovulation.
3. Sildenafil: Aids in increasing the thickness of uterus lining (off-label use).
4. Guaifenesin: May help thin the cervical mucus to aid in conception (off-label use).
5. Aspirin: Can be used before fertility procedures for uterine blood flow and decreased risk of ovarian hyperstimulation syndrome.

I. Complications: Ovarian Hyperstimulation Syndrome
1. What is it?
    a. Life-threatening complication of assisted conception
    b. Occurs in less than 4% of cycles for ovulation induction.
    c. About 1%–10% for in vitro fertilization
    d. Usually occurs in postovulatory stage.

2. What happens?
    a. Ovary enlargement
    b. Capillary permeability increase
    c. Protein-rich fluid escaping from the intravascular space to the extravascular space
    d. Patient may start to feel bloated; shortness of breath may occur; lethargy, nausea, vomiting, and diarrhea.
3. Clinical signs
    a. Rapid weight gain
    b. Ascites
    c. Pleural and pericardial effusions
    d. Oliguria or anuria
    e. Hemoconcentration
    f. Leukocytosis
    g. Hypovolemia, hyponatremia, hyperkalemia
    h. Adult respiratory distress syndrome
    i. Hypercoagulability
    j. Multiple organ failure
4. Who is at risk?
    a. Young age
    b. Low body weight
    c. High estradiol concentrations or rapidly increasing
    d. Size and number of follicles stimulated
    e. Number of eggs retrieved
    f. History of PCOS
5. Outpatient management
    a. Light physical activity
    b. Drink 1 L of fluid a day.
    c. Possibly withhold hCG injection to prevent it.
6. Hospital management
    a. Fluid management
    b. Thrombosis prophylaxis

J. Emotional Reactions to Infertility
1. Feelings of loss
2. Anger
3. Guilt
4. Shock
5. Lower self-esteem
6. Sexual dysfunction
7. Marital distress
8. Social isolation

K. Psychiatric Disorders
1. A reported 69% of women and 21% of men at a fertility clinic had a psychiatric disorder, possibly because of fertility issues, but exact reason unknown.
2. Depression
    a. Women with history of depression are twice as likely to have recurrence.
    b. Survey: 17% of women using assisted reproductive technique had depression.
3. Anxiety

4. Medication contribution: Fertility drugs affect mood.
    a. GnRH analogs, clomiphene can cause mood changes.
    b. Progesterone may induce depressive symptoms.
    c. Drugs may affect libido.

Patient Case

8. L.L. is a 26-year-old woman (height 61 inches, weight 78 kg) who has been trying to conceive for 13 months without success. She and her husband would like to conceive in the next year or so. Her BMI is 32 kg/m^2, and she has moderate acne and hirsutism. Her menstrual cycle is fairly regular at 26–27 days. Her husband's physical examination and semen analysis are normal. Her pelvic ultrasonography reveals polycystic ovaries, and she is given a diagnosis of PCOS.. Which is the best first-line agent to recommend to L.L. to help her conceive?

    A. Consider weight loss and start clomiphene tablets.

    B. Continue trying to conceive; make no recommendations at this time.

    C. Start FSH injections.

    D. Start hCG injections.

XIV. SEXUALLY TRANSMITTED INFECTIONS INCLUDING PELVIC INFLAMMATORY DISEASE, GYNECOLOGIC INFECTIONS

A. Herpes Simplex Virus (HSV) Infection
    1. Characteristics
        a. Types: HSV-1 and HSV-2 can cause genital herpes.
        b. Diagnosed in at least 50 million people in the United States
        c. Treatment can partly control symptoms but does not affect the risk, frequency, or severity of recurrences after it is discontinued.
        d. Symptoms include itching, genital burning, vesicle formation, and ulcer formation.
        e. After the primary infection, the virus is latent in the sacral dorsal root ganglia.
        f. From 50% to 80% of patients have recurrent infections (generally less severe and of shorter duration).
    2. Diagnosis
        a. Culture and polymerase chain reaction: Preferred
        b. Serologic testing
    3. Therapy
        a. Initial HSV infection
            i. Acyclovir 400 mg orally three times daily for 7–10 days
            ii. Acyclovir 200 mg orally five times daily for 7–10 days
            iii. Famciclovir 250 mg orally three times daily for 7–10 days
            iv. Valacyclovir 1 g orally twice daily for 7–10 days
        b. Recurrent HSV infection
            i. If treatment is initiated within 1 day of lesion onset, patients with recurrent infections may benefit.
                (a) Acyclovir 400 mg orally three times daily for 5 days
                (b) Acyclovir 800 mg orally three times daily for 2 days
                (c) Acyclovir 800 mg orally twice daily for 5 days
                (d) Famciclovir 125 mg orally twice daily for 5 days
                (e) Famciclovir 500 mg orally for 1 day; then 250 mg orally twice daily for 2 days
                (f) Famciclovir 1000 mg orally twice daily for 1 day

(g) Valacyclovir 500 mg orally twice daily for 3 days
(h) Valacyclovir 1000 mg orally once daily for 5 days

ii. Daily suppressive therapy recommended in patients with six or more episodes yearly (reassess annually the need for suppressive therapy)
(a) Acyclovir 400 mg orally twice daily
(b) Famciclovir 250 mg orally twice daily
(c) Valacyclovir 500 mg/day orally
(d) Valacyclovir 1000 mg/day orally

c. Severe disease (e.g. disseminated infection, pneumonitis, or hepatitis)
i. Should be hospitalized.
ii. Treatment: Acyclovir intravenously 5–10 mg/kg every 8 hours for 2–7 days, followed by oral antiviral therapy for at least 10 days of total therapy

4. Herpes encephalitis
a. Characteristics
i. Caused primarily by HSV-1
ii. Spreads through neural routes during primary or recurrent infection
iii. Primarily temporal lobe involvement with eventual hemorrhagic encephalitis
iv. Frequent neurologic sequelae, and high mortality if untreated
b. Diagnosis
i. Signs and symptoms (nonspecific)
(a) Headache
(b) Fever
(c) Speech disorders and behavioral changes
(d) Focal seizures
ii. Cerebrospinal fluid analysis
(a) Moderate pleocytosis (generally lymphocytosis)
(b) Normal glucose and moderately elevated protein
iii. Brain biopsy (rarely performed)
c. Therapy: Treatment should be intravenous acyclovir for 21 days.

Patient Case

Questions 9 and 10 pertain to the following case:

D.H. is a 21-year-old woman who presents to the clinic with genital itching and vesicles on her vulva. She is sexually active with one partner who has a history of herpes. Her partner does not always use a condom when they have sex. She is initiated on acyclovir for this initial HSV infection.

9. Which statement is best to mention to D.H. regarding the treatment of her herpes infection?
A. Treatment of the initial infection will decrease the risk of recurrent herpes infections.
B. Treatment will shorten the duration of symptoms and infectivity of the initial infection.
C. Treatment of the initial infection will decrease the severity of recurrent herpes infections.
D. Treatment of the initial infection will prevent the virus from remaining latent in the dorsal root ganglia.

Patient Case *(continued)*

10. D.H. returns to the clinic 10 months after her initial herpes infection. She is troubled by all the recurrences she is having (seven to date). Which therapy is best to recommend?
    A. Valacyclovir 500 mg orally twice daily to be used for 5 days whenever she notices a recurrence beginning.
    B. Acyclovir 400 mg orally three times daily to be used for 10 days whenever she notices a recurrence beginning.
    C. Suppressive therapy with famciclovir 250 mg orally three times daily.
    D. Suppressive therapy with valacyclovir 500 mg daily orally.

B. Syphilis (*Treponema pallidum*)
    1. Diagnosis
        a. Dark-field examination and direct fluorescent antibody stains of exudate for spirochetes
        b. Nontreponemal (Venereal Disease Research Laboratory and Rapid Plasma Reagin); detect serum concentrations of antibody to cardiolipin.
        c. Treponemal (fluorescent treponemal antibodies and *T. pallidum* particle agglutination test): Detect antibodies to *T. pallidum*.
        d. In general, perform a nontreponemal test for screening purposes and confirm with a treponemal test.
    2. Primary syphilis
        a. From 10 to 90 days after exposure (mean 21 days)
        b. The primary symptom is the development of a chancre.
        c. The chancre resolves spontaneously in 2–6 weeks, even without treatment.
        d. Recommended treatment
            i. Benzathine penicillin G 2.4 million units intramuscularly in a single dose (adults)
            ii. If penicillin allergy: Doxycycline 100 mg orally twice daily or tetracycline 500 mg four times daily for 2 weeks
    3. Secondary syphilis or early latent syphilis
        a. 4–10 weeks after exposure
        b. Skin lesions: Characteristically on the palms and soles
        c. Latent phase begins when all symptoms have resolved.
        d. Recommended treatment
            i. Benzathine penicillin G 2.4 million units intramuscularly in a single dose
            ii. If penicillin allergy: Doxycycline 100 mg orally twice daily or tetracycline 500 mg four times daily for 28 days
    4. Late latent syphilis
        a. More than 1 year in duration or unknown duration
        b. Recommended treatment
            i. Benzathine penicillin G 2.4 million units intramuscularly every week for 3 weeks
            ii. If penicillin allergy: Doxycycline 100 mg twice daily or tetracycline 500 mg four times daily for 4 weeks
    5. Tertiary syphilis
        a. Infectious granulomas and cardiovascular effects: Aortic insufficiency and aortitis
        b. Recommended treatment
            i. Benzathine penicillin G 2.4 million units intramuscularly every week for 3 weeks
            ii. If penicillin allergy: Treat in consultation with an infectious disease specialist.

6. Neurosyphilis
    a. Recommended treatment: Aqueous crystalline penicillin G 3–4 million units intravenously every 4 hours or continuous infusion (total of 18–24 million units per day) for 10–14 days
    b. Alternative regimen
        i. Procaine penicillin 2.4 million units/day intramuscularly plus probenecid 500 mg four times daily for 10–14 days
        ii. If penicillin allergy: Ceftriaxone 2 g/day intramuscularly/intravenously for 10–14 days, or patients should be desensitized and given penicillin (see CDC recommendations for skin testing and desensitization).
7. Treatment of sexual partners
    a. Sexual partners should be presumptively treated if exposed within 90 days preceding the diagnosis in their partner.
    b. If exposure occurred more than 90 days prior, sexual partners should be tested and monitored closely or treated presumptively if serologic test results are not available immediately.

C. Chlamydial Infection
1. Can lead to PID, ectopic pregnancy, and infertility
2. Less dysuria and penile discharge in men compared with gonococcal infection
3. Diagnosis
    a. Nucleic acid amplification testing (NAAT)
        i. Preferred method, recommended in 2015 CDC guidelines
        ii. Allows for a wide variety of FDA-cleared specimen types such as vaginal swabs, urethral swabs, endocervical, and urine
    b. Culture
        i. Requires endocervical swab (women)
        ii. Requires urethral swab (men)
4. Treatment
    a. Azithromycin 1 g in a single dose or doxycycline 100 mg twice daily for 7 days
    b. Alternatives: Erythromycin base 500 mg orally four times daily for 7 days, ofloxacin 300 mg orally twice daily for 7 days, levofloxacin 500 mg/day orally for 7 days, or erythromycin ethylsuccinate 800 mg orally four times daily for 7 days
    c. Abstain from sexual intercourse for at least 7 days and until sexual partners are adequately treated.
    d. All sexual partners within the past 60 days should be assessed and treated.

D. Gonococcal Infection
1. Penile discharge and dysuria common in men, but women are often asymptomatic (which can lead to PID); symptoms in women include vaginal discharge and dysuria.
2. Diagnosis
    a. Nucleic acid amplification testing (NAAT)
        i. Preferred method; recommended in 2015 CDC guidelines
        ii. Allows for a wide variety of FDA-cleared specimen types such as vaginal swabs, urethral swabs, endocervical, and urine
    b. Culture
        i. Requires endocervical swab (women)
        ii. Requires urethral swab (men)

3. Treatment
    a. Uncomplicated gonococcal infections of cervix, urethra, and rectum: Ceftriaxone 250 mg intramuscularly plus azithromycin 1 g in a single dose. Provides dual gonococcal coverage to slow emerging resistance and co-treatment for chlamydia. Alternative if ceftriaxone not an option, cefixime 400 mg orally as single-dose plus azithromycin 1 g in a single dose and test for cure in 14 days. Doxycycline no longer recommended in place of azithromycin because of gonococcal resistance
    b. Gonococcal infection of the pharynx: Ceftriaxone plus azithromycin 1 g in a single dose
    c. Allergy to cephalosporins, may consider dual treatment with single dose of intramuscular gentamicin 240 mg plus azithromycin 2 g orally. Should consult an infectious disease specialist if patient has a cephalosporin allergy or immunoglobulin E–mediated penicillin allergy
    d. Abstain from sexual intercourse for at least 7 days and until sexual partners are adequately treated.
    e. All sexual partners within the past 60 days should be assessed and treated.

E. Urethritis
1. Undiagnosed: Treat for both chlamydia and *Gonococcus*.
2. Nongonococcal
    a. Treat for chlamydia.
    b. Also consider *Mycoplasma genitalium*.
        i. Responsible for 15%–20% of nongonococcal urethritis (NGU), 20%–25% of non-chlamydial NGU, and about 30% of persistent or recurrent urethritis
        ii. Treatment: Lacks a cell wall, so ß-lactams are ineffective, high resistance for doxycycline, and emerging resistance for azithromycin. Recommendation is moxifloxacin 400 mg orally daily for 7, 10, or 14 days.
3. Recurrent or persistent: Ensure adherence and no reinfection from infected partner; if these are ensured, treat with metronidazole or tinidazole for *Trichomonas vaginalis* and azithromycin.
4. All sexual partners within the past 60 days should be assessed and treated.

F. Pelvic Inflammatory Disease
1. Ascending infection of the female genital tract involving primarily the fallopian tubes
2. Clinical presentation
    a. Lower abdominal tenderness
    b. Adnexal tenderness
    c. Cervical motion tenderness
    d. Oral temperature greater than 101°F
    e. Abnormal cervical or vaginal discharge
    f. Elevated erythrocyte sedimentation rate
    g. Elevated C-reactive protein
    h. Menorrhagia
    i. Dysuria
3. Sequelae: Abscess in pelvic or fallopian tubes, tubal occlusion, fibrosis, infertility; PID leads to infertility and ectopic pregnancies.
4. In general, sexually transmitted and caused by *Neisseria gonorrhoeae, Chlamydia trachomatis,* anaerobes, gram-negative facultative bacteria, and streptococci.

5. Treatment
    a. Parenteral treatment
        i. Regimen A: Cefotetan 2 g intravenously every 12 hours or cefoxitin 2 g intravenously every 6 hours plus doxycycline 100 mg intravenously or orally every 12 hours. Parenteral therapy can be discontinued 24–48 hours after clinical improvement and changed to oral therapy for 14 days.
        ii. Regimen B: Clindamycin 900 mg intravenously every 8 hours plus gentamicin intravenously or intramuscularly 2-mg/kg loading dose; then 1.5 mg/kg every 8 hours (or once-daily therapy with 3- to 5-mg/kg dosing). Parenteral therapy can be discontinued 24 hours after clinical improvement and changed to oral therapy for 14 days.
        iii. Alternative regimens: Ampicillin/sulbactam 3 g intravenously every 6 hours plus doxycycline 100 mg intravenously or orally every 12 hours
    b. Intramuscular/oral treatment:
        i. Regimen A: Ceftriaxone 250 mg intramuscularly once plus doxycycline 100 mg twice daily for 14 days with or without metronidazole 500 mg orally twice daily for 14 days
        ii. Regimen B: Cefoxitin 2 g intramuscularly and probenecid 1 g orally plus doxycycline 100 mg twice daily for 14 days with or without metronidazole 500 mg orally twice daily for 14 days
    c. Treatment for *M. genitalium* should be considered if PID treatment for 7–10 days has failed. Recommended to start moxifloxacin 400 mg orally daily for 14 days.
    d. Sexual partners of patients with PID within the past 60 days should be tested and treated.

Patient Case

Questions 11 and 12 pertain to the following case:

M.A. is a 24-year-old woman who presents to the emergency department with severe abdominal pain, fever, dysuria, and a vaginal discharge. She is sexually active with many male partners. Her medical history is unremarkable except for recurrent genital herpes (one or two episodes a year). Her medications on admission include birth control pills (ethinyl estradiol 30 mcg/desogestrel 0.15 mg) and fluticasone nasal spray as needed. On physical examination, M.A.'s vital signs include temperature 101.2°F (38°C), heart rate 92 beats/minute, respiration rate 15 breaths/minute, and blood pressure 117/75 mm Hg. M.A. has adnexal tenderness, cervical motion tenderness, and a vaginal discharge.

11. Which is the best empiric therapy for M.A.?
    A. Ampicillin/sulbactam intravenously 2 g every 6 hours for 14 days
    B. Metronidazole 500 mg intravenously three times daily for 7 days
    C. Cefotetan 2 g intravenously every 12 hours with doxycycline 100 mg orally every 12 hours for 14 days
    D. Ceftriaxone 125 mg intramuscularly once with doxycycline 100 mg intravenously twice daily for 7 days

12. Which statement is best for M.A. to tell her sexual partners?
    A. There is no need for concern because this condition is not transmittable to or acquired from a sexual partner.
    B. Her partner can resume having sexual intercourse with M.A. as soon as her symptoms improve.
    C. If her partner has had sex with M.A. within the past 60 days, he should be assessed for possible treatment.
    D. Her partner does not need to be tested for human immunodeficiency virus (HIV) because there is no relationship between HIV and this condition.

G. Bacterial Vaginosis
   1. Malodorous vaginal discharge caused by an overgrowth of anaerobic bacteria (circumventing the normal flora of *Lactobacillus*); more than 50% with bacterial vaginosis are asymptomatic.
   2. Infection risk is increased in relation to sexual activity, but it is unknown whether acquired through sexual partner.
   3. Diagnosis is based on a malodorous vaginal discharge that is high in pH, contains clue cells, and is whiff test positive (fishy odor after potassium hydroxide 10% added to sample).
   4. Bacterial vaginosis has been implicated in PID and is possibly linked to endometritis.
   5. Treatment
      a. Nonpregnant women: Metronidazole 500 mg orally twice daily for 7 days or clindamycin 2% cream, 1 full applicator intravaginally at bedtime for 7 days, or metronidazole 0.75% gel, 1 full applicator intravaginally once daily for 5 days
      b. Alternatives: Clindamycin ovules 100 mg intravaginally at bedtime for 3 days, clindamycin 300 mg orally twice daily for 7 days, tinidazole 2 g orally once daily for 2 days, tinidazole 1 g orally once daily for 5 days, secnidazole (Solosec) 2 g packet of granules, sprinkle on pudding, applesauce, or yogurt (do not chew or crush granules, do not dissolve in a liquid) and consume within 30 minutes
      c. Pregnant women: Oral or vaginal therapy regimens of metronidazole or clindamycin
      d. Treatment of sexual partners is not necessary.

H. Trichomoniasis
   1. Caused by *T. vaginalis*
   2. Men often have no symptoms, but women generally have a malodorous, yellow-green vaginal discharge and vaginal irritation.
   3. Diagnosis most sensitive with NAAT, many times detecting five times more *T. vaginalis* infections than wet-mount microscopy.
   4. Treatment
      a. Metronidazole 2 g orally in a single dose or tinidazole 2 g orally in a single dose
      b. Alternative: Metronidazole 500 mg orally twice daily for 7 days
      c. All sexual partners should be treated.
      d. Metronidazole-allergic patients should be desensitized.

I. Vulvovaginal Candidiasis
   1. Seventy-five percent of women have at least one episode (40%–45% will have many episodes).
   2. Symptoms include pruritus and vaginal discharge.
   3. Predisposing factors include OCs, pregnancy, obesity, diabetes mellitus, corticosteroid use, chemotherapy, and antibiotics.
   4. Diagnosed by symptoms and potassium hydroxide smear

5. Therapeutic regimens: 1- and 3-day regimens may take up to 7 days for full effect (Table 19).

Table 19. Therapeutic Regimens for Treatment of Vulvovaginal Candidiasis

Drug	Dose	Length of Therapy
Butoconazole	2% cream: 5 g intravaginally	1 dose
Clotrimazole	1% cream: 5 g intravaginally at bedtime (OTC)	7–14 days
	2% cream: 5 g intravaginally at bedtime (OTC)	3 days
Miconazole	2% cream: 5 g intravaginally at bedtime (OTC)	7 days
	4% cream: 5 g intravaginally at bedtime (OTC)	3 days
	100-mg vaginal suppository at bedtime (OTC)	7 days
	200-mg vaginal suppository at bedtime (OTC)	3 days
	1200-mg vaginal suppository × 1 (OTC)	1 dose
Terconazole	0.4% cream: 5 g intravaginally at bedtime	7 days
	0.8% cream: 5 g intravaginally at bedtime	3 days
	80-mg vaginal suppository at bedtime	3 days
Tioconazole	6.5% ointment: 5 g intravaginally (OTC)	1 dose
Fluconazole	150-mg oral tablet	1 dose

OTC = over the counter

6. Recurrent vulvovaginal candidiasis (four or more episodes a year): Needs prescription drug treatment, not OTC.
   a. Initial treatment for 7–14 days or fluconazole 100-, 150-, or 200-mg dose every third day for three doses
   b. Maintenance: Oral fluconazole 100, 150, or 200 mg/week for 6 months
   c. Consider conditions precipitating recurrent vulvovaginal candidiasis: HIV, diabetes mellitus.
7. Prophylaxis needed for vulvovaginal candidiasis while taking antibiotics; recommend OTC 7-day treatment and use a full applicator at bedtime while taking antibiotics; oral fluconazole is also sometimes used.
8. Pregnant women: Drugs of choice are topical azoles, 7-day treatment.

XV. PROSTATIC INFECTIONS

A. Prostatitis
   1. Symptoms
      a. Urethritis
      b. Asymptomatic
      c. Primarily gram-negative organisms: *C. trachomatis, N. gonorrhoeae, Escherichia coli*
   2. Acute bacterial prostatitis
      a. Therapy duration: 14–28 days
      b. Depends on organism
         i. Ceftriaxone 250 mg intramuscularly for gonorrhea
         ii. Fluoroquinolones: Ciprofloxacin 500 mg twice daily, levofloxacin 500–750 mg once daily, ofloxacin 400 mg twice daily
         iii. Cotrimoxazole (trimethoprim/sulfamethoxazole DS [TMP 160 mg/SMX 800 mg]) twice daily or trimethoprim 200 mg twice daily

3. Chronic bacterial prostatitis (symptoms should have been present for at least 6 months)
    a. Therapy duration: 28 days, may be longer up to 6 weeks and in some refractory cases 6–12 weeks
    b. Depends on organism
        i. Fluoroquinolones: Ciprofloxacin 500 mg twice daily, levofloxacin 500–750 mg daily, ofloxacin 200 mg twice daily, norfloxacin 400 mg twice daily (not for gonorrhea)
        ii. Minocycline 100 mg twice daily, doxycycline 100 mg twice daily, trimethoprim 200 mg twice daily, cotrimoxazole (TMP/SMX) DS twice daily

B. Epididymitis
    1. Initial therapy: If caused by gonococcal or chlamydial infection, ceftriaxone 250 mg intramuscularly once plus doxycycline 100 mg twice daily for 10 days
    2. If caused by enteric organisms:
        a. Ofloxacin 300 mg twice daily orally for 10 days (not for gonorrhea)
        b. Levofloxacin 500 mg/day orally for 10 days (not for gonorrhea)

XVI. MALE SEXUAL DYSFUNCTION

A. Types
    1. Reduced libido from organic or psychological causes
        a. Low serum testosterone concentrations
        b. Elevated concentrations of serum prolactin
    2. Ejaculation
        a. Premature
        b. Retarded
        c. Absent
        d. Retrograde
    3. Erectile dysfunction
        a. Persistent (at least 6 months) inability to achieve or maintain an erection of sufficient duration and firmness to complete satisfactory intercourse through vaginal penetration
        b. Psychological
        c. Organic
        d. Mixed
        e. Causes
            i. Vasculogenic
                (a) CVD (hypertension, coronary artery disease)
                (b) Diabetes mellitus
                (c) Hyperlipidemia
                (d) Smoking
                (e) Major pelvic surgery or radiotherapy
            ii. Neurogenic
                (a) Central causes: Degenerative disorders, spinal cord trauma or disorders, stroke, CNS tumors
                (b) Peripheral causes: Type 1 or 2 diabetes, chronic renal failure, neuropathy, abdominal surgery, or urethral surgery
            iii. Hormonal abnormalities because of excess prolactin (hyperprolactinemia) or decreased testosterone concentrations (hypogonadism), hyperthyroidism or hypothyroidism, hypercortisolism or hypocortisolism

iv. Medical conditions such as angina, shortness of breath because of asthma or chronic obstructive pulmonary disease
v. Drugs such as antihypertensives, psychiatric medications (antidepressants and antipsychotics), antiandrogens, recreational drugs
vi. Anatomical
(a) Hypospadias
(b) Micropenis
(c) Peyronie's disease
vii. Trauma: Penile fracture, pelvic fracture

B. Treatment of Erectile Dysfunction
1. Control risk factors
a. Stop smoking.
b. Control diabetes mellitus. Check A1C and fasting blood glucose.
c. Control hyperlipidemia.
d. Control hypertension.
e. Decrease alcohol intake.
f. Discontinue illicit drugs.
g. Lose weight.
h. Exercise.
i. Review current medications.
j. CVD must be stabilized and assessed before treatment; must assess whether sexual activity in stable relationship does not increase risk of cardiovascular events or put undue stress on heart.
k. Physical exam
l. Mental health evaluation
2. Nonpharmacologic treatment
a. Vacuum pump devices (may cause adverse effects such as pain and bruising)
b. Venous constriction rings (may cause adverse effects such as pain and bruising)
c. Shockwave therapy
d. Penile implant
e. Counseling
3. Testosterone replacement if testosterone concentrations are low
a. Oral testosterone, Jatenzo oral capsules: Recommended dosage is 237 mg by mouth in the morning and evening with food. May decrease dose to 158 mg twice daily or maximal dose of 396 mg twice daily, depending on testosterone concentration obtained 6 hours after the morning dose after 7 days of administration.
b. Depot intramuscular injection of testosterone enanthate 200 mg or cypionate 300 mg every 2–4 weeks, undecanoate initially 4 weeks after first injection; then every 10 weeks
c. Transdermal patches placed daily: Androderm 2–6 mg at bedtime on back, abdomen, or arms; rotate sites; available in 2 mg/day and 4 mg/day transdermal systems
d. Testosterone gel applied every morning
i. Testim 1% has 50 mg of testosterone per tube; apply to shoulders, upper arms only.
ii. AndroGel 1.62% packets, 20.25 mg and 40.5 mg of testosterone or in a pump; 2 pumps = 40.5 mg of testosterone and should be applied once daily in the morning.
iii. AndroGel 1% packets available in 25 mg and 50 mg of testosterone or in a pump; 4 pumps = 50 mg of testosterone that should be applied once daily in the morning; may be applied to shoulders, upper arms, and abdomen; should not be applied to genitals, chest, or back.

iv. Fortesta 2% gel, may apply 10–70 mg; 1 pump = 10 mg; apply to thighs; avoid genitals.
v. Vogelxo 1% 50 mg/one tube or packet and Vogelxo 1% Pump (4 actuations, 1 actuation = 12.5 mg); apply to clean, dry, intact skin of shoulders or upper arms; do not apply to genitals or abdomen.

e. Axiron topical solution, apply 60 mg (1 actuation = 30 mg) to underarms once daily.
f. Testopel 75-mg pellet, implanted; provides hormone for 3–4 months.
g. Striant 30-mg buccal system; placed on gum tissue above incisors with flat section facing cheek; used twice daily.
h. Natesto nasal gel, recommended dosage is 11 mg of testosterone (5.5 mg/actuation, 2 pump actuations, 1 per nostril) applied intranasally three times daily; should not be administered with sympathomimetic decongestants (e.g., oxymetazoline).
i. Adverse effects and contraindications
    i. Contraindicated in patients with prostate cancer
    ii. Patches may cause redness and irritation at site of application.
    iii. May cause increase in blood pressure, acne, enlarged prostate, liver toxicity, cholesterol changes, edema, polycythemia.
j. Monitor serum testosterone within 1–3 months and at 6- to 12-month intervals.
k. If no improvement after 3 months, may discontinue treatment.
l. The 2020 ACP guidelines recommend the following:
    i. Discussions of testosterone treatment in men with age-related low testosterone and sexual dysfunction should include the potential benefits, harms, costs, and patient preferences.
    ii. Symptoms should be reevaluated within 12 months (and then periodically). Testosterone should be discontinued if sexual function does not improve.
    iii. Given lower costs, intramuscular testosterone rather than transdermal should be considered. Efficacy and risk profiles are similar between the formulations.

4. Phosphodiesterase (PDE) inhibitors (first-line drug therapy for men without contraindications to use) (Table 20)
    a. Sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra/Staxyn), avanafil (Stendra)
    b. Inhibits PDE-5 in the penile tissue, preventing the breakdown of cyclic guanosine monophosphate, thus increasing smooth muscle relaxation in the corpora cavernosa and increasing penile rigidity.
    c. Adverse effects: Headache, hot flashes, heartburn, diarrhea, myalgias, hypotension, dizziness, difficulty discriminating blue from green
    d. Contraindications, cautions, and drug interactions
        i. Contraindicated with nitrate use; should not be used together.
        ii. Use caution with CVD, hypotension, uncontrolled hypertension, MI, or stroke within 6 months, life-threatening arrhythmias, penile deformities, renal or hepatic dysfunction, and degenerative retinal disorders.
        iii. Drug interactions such as protease inhibitors; decrease PDE inhibitor dosage by half in some cases; precautions with CYP3A4 inhibitors and macrolides because they increase PDE inhibitor levels; may also need to decrease PDE inhibitor doses in these situations or possibly avoid combined use with CYP3A4 inhibitors.
    e. Doses
        i. Sildenafil 50 mg orally; maximal dose 100 mg/day, usually take tablet 1 hour before intercourse
        ii. Tadalafil 10 mg orally; maximal dose 20 mg/day; effects may last up to 36 hours; may also use as daily dose without respect to timing of intercourse, tadalafil 2.5–5 mg orally daily (also has indication for benign prostatic hypertrophy but should not be used with α-blockers such as doxazosin; may result in hypotension)

iii. Vardenafil 10 mg orally; maximal dose 20 mg/day, usually take tablet 30 minutes to 1 hour before intercourse
iv. Avanafil 100 mg orally; maximal dose 200 mg/day; also may lower dosage to 50 mg/day if needed, but initial recommendation is to start with 100 mg orally per day; usually take tablet 30 minutes before intercourse

Table 20. Summary of Phosphodiesterase-5 Medications

Name	Dosage	Comments
Sildenafil (Viagra)	50 mg PO 1 hr before intercourse (dose range 25–100 mg)	May require hepatic and renal dosage adjustments Take on empty stomach
Vardenafil (Levitra)	10 mg PO 1 hr before intercourse (dose range 5–20 mg)	May require hepatic dosage adjustment Fatty meal delays onset
Vardenafil oral disintegrating tablet (Staxyn)	10 mg PO 1 hr before intercourse	Not recommended with hepatic conditions Do not use with CYP3A4 inhibitors
Tadalafil (Cialis)	5 mg PO up to 36 hr before intercourse (dose range 5–20 mg) 2.5–5 mg PO daily for daily dosing	May require hepatic or renal dose adjustments Food has no effect on onset
Avanafil (Stendra)	100 mg PO 30 min before intercourse (dose range 50–200)	Fatty food may delay onset

PO = by mouth

5. Alprostadil (second-line therapy if PDE-5 inhibitors fail)
   a. Caverject intracavernosal injection 2.5–40 mcg
   b. MUSE urethral pellets 125–1000 mcg
   c. Effect may last 30–90 minutes.
   d. Adverse effects: Penile pain, cavernosal scarring, priapism, hypotension
   e. Drug interactions: Do not use with PDE inhibitors.
6. Yohimbine
   a. Derivative of African yohimbine tree
   b. α_2-Antagonist
   c. Efficacy controversial; not recommended according to the American Urological Association guidelines.
   d. Adverse effects: Headaches, dizziness, insomnia, and anxiety
   e. Dose: 5.4 mg orally three times daily

C. Treatment of Premature Ejaculation
   1. Antidepressants: Off-label use
      a. Selective serotonin reuptake inhibitors: Fluoxetine, paroxetine, sertraline
      b. Tricyclic antidepressant: Clomipramine
      c. Continuous (daily), or episodic dosing 2–12 hours before intercourse
   2. Topical anesthetics: Lidocaine/prilocaine cream (EMLA [eutectic mixture of local anesthetic]) 2.5 g applied to the glans penis and penile shaft 20–30 minutes before intercourse

Patient Case

13. A 65-year-old man presents to his physician with symptoms that are determined to be erectile dysfunction. He has a history of hyperlipidemia, gastroesophageal reflux disease, and glucose intolerance. His medications include atorvastatin 40 mg orally daily, omeprazole 20 mg orally daily, and aspirin 81 mg orally daily as tolerated. He states that he has heard of medications to help with his symptoms but does not want to have to plan his intimate moments. Which drug would work best for this patient?

    A. Tadalafil

    B. Avanafil

    C. Yohimbine

    D. Bupropion

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

DVT is increased with conjugated estrogens and medroxyprogesterone acetate (Prempro) (Answer A is correct). Myocardial infarction and strokes are also increased (Answers B and C are incorrect). Fractures are decreased (Answer D is incorrect).

2. Answer: C

The patient has an intact uterus; therefore, she needs both an estrogen and a progestogen. Conjugated estrogens and medroxyprogesterone acetate (Prempro) is the only product listed that includes a progestogen (Answer C is correct). The patient has hot flashes in addition to vaginal dryness; therefore, a systemic product is recommended (Answer B is incorrect). A vaginal insert or cream would be appropriate for GSM symptoms but not for hot flashes, and ospemifene is indicated for vaginal atrophy. The patch would be appropriate if a progestogen were added to the regimen (Answers A and D are incorrect).

3. Answer: C

The definitions of bone mineral density and T-scores are as follows:

Normal = BMD within 1 standard deviation (SD) of the young adult mean, Low bone mass (osteopenia) = BMD between -1 SD and -2.5 SD,

Osteoporosis = BMD at least -2.5 SD,

Severe osteoporosis = BMD less than -2.5 and history of a fracture. The patient has a T-score of -2.6 at the hip, which is indicative of osteoporosis (Answer C is correct; Answers A and B are incorrect). The patient does not have severe osteoporosis of the spine because her T-score at the spine is -2.1 and not less than -2.5 (Answer D is incorrect).

4. Answer: D

Drug therapy is indicated for the following: A hip or vertebral fracture; a BMD T-score below -2.5 at the femoral neck or spine, excluding secondary causes; or a BMD T-score between -1.0 and -2.5 at the femoral neck or spine and a 10-year probability of hip fracture 3% or greater or a 10-year probability of major osteoporosis-related fracture of 20% or greater based on the FRAX system. The patient needs therapy because her T-score is less than -2.5 at the hip, and her 10-year probability of hip fracture is at least 3% or her 10-year probability of major osteoporosis-related fracture at least 20% based on the FRAX system (Answer D is correct; Answer A is incorrect). Bisphosphonates such as alendronate and risedronate are considered first-line drugs because they inhibit normal and abnormal bone resorption and reduce vertebral and non-vertebral fractures by 30%–50%. For risendronate, the treatment dosage is 35 mg orally weekly, further indicating that Answer D is correct. In addition, the patient's CrCl is 60–70 mL/minute/1.73 m^2, which allows use of a bisphosphonate. Use of a bisphosphonate is contraindicated at a CrCl less than 30–35 mL/minute/1.73 m^2. Abaloparatide (Tymlos) is reserved for treating women at a high risk of fracture, including those with a very low BMD (T-score less than -3.0) and a previous vertebral fracture (Answer B is incorrect). The patient should receive vitamin D 800 international units daily because she is older than 70 years and takes calcium 1200 mg daily in divided doses (again, Answer D is correct; Answers A and B are incorrect). In addition, the patient is likely not receiving calcium from her diet due to her lactose intolerance and minimal intake of dairy products. Romosozumab is not indicated as first-line treatment and is indicated for those at high risk of fracture, those with a previous fracture, or those for whom other osteoporosis therapies have failed (Answer C is incorrect).

5. Answer: C

Lisinopril is an ACE inhibitor known to have some teratogenicity. It is not recommended for women who are trying to conceive or who are pregnant (Answers A and D are incorrect). This patient needs treatment for hypertension, particularly while pregnant, because hypertension can lead to detrimental effects in the fetus and mother (Answer B is incorrect). Labetalol and nifedipine are the preferred agents for treating hypertension in women who are trying to conceive or pregnant, with labetalol used more often in recent years (Answer C is correct). β-Blockers are not specifically teratogenic but may cause adverse effects in the fetus such as intrauterine growth retardation, particularly with atenolol (Answer D is incorrect). Diuretics such as hydrochlorothiazide are not first line. They can be used as a second- or third-line agent. (again, Answer A is incorrect).

6. Answer: B
Estrogen deficiency causes early or midcycle breakthrough bleeding (days 1–14). There is possible deficiency in estrogen and progestin at mid-cycle. Progestin deficiency results in late breakthrough bleeding (days 14–28). An OC with stronger estrogenic properties is needed because the patient is bleeding through early in the cycle. Ethinyl estradiol 30 mcg/desogestrel 0.3 mg (Reclipsen) has higher estrogenic properties (intermediate) than ethinyl estradiol 20 mg/levogestrel 0.1 mg (Lessina) while the other OC options have low estrogenic properties (Answer B is correct; Answers C and D are incorrect). The patient has been using Lessina for 4 months, which is past the trial period of 3 months, with continued breakthrough bleeding. Therefore, the patient could switch to another product (Answer A is incorrect).

7. Answer: C
Estrogen-containing products (ethinyl estradiol/drospirenone and contraceptive patch) are contraindicated for this patient because she is a smoker older than 35. In addition, the patient cannot use the contraceptive patch (ethinyl estradiol and norelgestromin [Xulane]) because her weight is more than 90 kg. Even though she smokes only ½ pack of cigarettes per day, her other risk factors such as age and hypertension increase the risk of events with tobacco use. In addition, she takes an ACE inhibitor, which would not be the best choice with drospirenone because of the possibility of hyperkalemia (Answer B is incorrect). Depot medroxyprogesterone acetate has a long return to fertility time, and the patient is 37 years old (Answer D is incorrect). Moreover, DMPA may cause weight gain, and the patient already has obesity. Norethindrone has a quick return to fertility and will not affect her hypertension or interact with her ACE inhibitor (Answer C is correct).

8. Answer: A
The patient has obesity, with a BMI of 32 kg/m^2. To optimize her chances of ovulation, she should try to lose weight and lower her BMI. Her ultrasonography, hirsutism, and acne indicate she has PCOS. Clomiphene citrate would be a first-line agent to help stimulate ovulation (Answer A is correct). She and her husband have been trying to conceive for 13 months, which meets the definition of infertility necessitating intervention (Answer B is incorrect). Human chorionic gonadotropin injections are not appropriate to provide at this time; they are usually used to help the ovum rupture once the follicle has been stimulated to increase (Answer D is incorrect). Follicle-stimulating hormone would not be recommended at this time as it is not a first-line treatment (Answer C is incorrect). If the patient fails clomiphene or letrozole (another option instead of clomiphene but not an option in the answers) then FSH injections might be appropriate at that time.

9. Answer: B
Treatment of HSV infection substantially decreases the duration of viral shedding, pain, and time to complete healing but does not affect the risk, frequency, latency, or severity of recurrences (Answer B is correct; all others are incorrect).

10. Answer: D
Patient-initiated therapy is important for people with occasional recurrences (fewer than six per year) of HSV infection because recurrent infections resolve more rapidly than the initial infection. Antiviral agents should be initiated as soon as possible. Because the patient is having several recurrences (six or more a year), patient-initiated therapy is insufficient (Answers A and B are incorrect). Suppressive therapy is given twice daily or once daily, not three times daily; therefore, suppressive therapy with famciclovir 250 mg orally three times daily is inappropriate (Answer C is incorrect). Suppressive therapy with valacyclovir 500 mg/day orally should be offered (Answer D is correct).

11. Answer: C
Cefotetan 2 g intravenously every 12 hours with doxycycline 100 mg orally or intravenously every 12 hours is an appropriate empiric antibiotic combination for PID (Answer C is correct). The combination has activity against *N. gonorrhoeae* and *C. trachomatis* and against the gram-negative and anaerobic organisms that are often involved. Metronidazole alone would have activity only against anaerobes and would miss the other organisms often involved in PID (Answer B is incorrect). Ampicillin/sulbactam has good activity against most organisms in PID; however, it has no activity against atypical organisms (e.g., *C. trachomatis*) (Answer A is incorrect). Although ceftriaxone and doxycycline are appropriate, the ceftriaxone dosage should be 250 mg, and the duration of doxycycline should be 14 days (Answer D is incorrect).

12. Answer: C

Pelvic inflammatory disease is related to sexual activity; therefore, until all partners and the patient have been treated, abstinence from intercourse for at least 7 days is indicated, (Answers A and B are incorrect). Patients should be encouraged to be tested for HIV because of the strong relationship between STDs and the risk of HIV (Answer D is incorrect). The most appropriate recommendation for a sexually active patient with PID is to have all sexual partners within the past 60 days tested and treated (Answer C is correct).

13. Answer: A

Tadalafil may be dosed daily without respect to timing of sexual intercourse (Answer A is correct). Avanafil should be taken 30 minutes before sexual intercourse (Answer B is incorrect). Yohimbine and bupropion are not first line for erectile dysfunction (Answers C and D are incorrect). Bupropion is usually used in women with sexual dysfunction caused by serotonin reuptake inhibitors and not usually used in men for the treatment of sexual dysfunction.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A
The patient's T-score at the hip and spine are between -1 and -2.5 SD, which is considered low bone mass (Answer A is correct). Normal BMD is defined as a T-score within 1 SD of the young adult mean, which the patient does not have (Answer D is incorrect). Osteoporosis is defined of having BMD with a T-score of at least -2.5 SD, which the patient does not have in either the hip or the spine (Answers B and C are incorrect).

2. Answer: A
Even though the patient is currently thought to have osteopenia, his 10-year probability of a major osteoporosis-related fracture is 14%, and his 10-year probability of a hip fracture is 6.7% according to the FRAX score, which indicates a need for drug therapy (Answer A is correct). Bisphosphonates such as alendronate and risendronate are considered first-line drugs because they inhibit normal and abnormal bone resorption and reduce vertebral and non-vertebral fractures by 30%–50%. Raloxifene is indicated for preventing osteoporosis in postmenopausal women. It works as a selective estrogen receptor modulator and is best for preventing vertebral fractures, not hip fractures (Answer C is incorrect). Calcium and vitamin D are both recommended for this patient as well. Because of the patient's age and poor diet, the recommended dosage of vitamin D is 800 international units orally per day (Answer A is correct; Answer D is incorrect); 600 international units orally per day is recommended for those younger than 70 years (Answer B is incorrect). Answer B is also incorrect because the patient requires pharmacotherapy and not just calcium and vitamin D. He walks 30 minutes/day, which satisfies the recommendation of weight-bearing activity (Answers B and D are incorrect).

Drug therapy begins with the following:

(a) A hip or vertebral fracture

(b) BMD T-score below -2.5 at the femoral neck or spine, excluding secondary causes

(c) BMD T-score between -1.0 and -2.5 at the femoral neck or spine and a 10-year probability of hip fracture 3% or greater or 10-year probability of major osteoporosis-related fracture 20% or greater according to the FRAX system.

3. Answer: C
Warfarin is contraindicated in pregnancy and a known teratogen (Answers A, B, and D are incorrect). Warfarin should not be used at any time during pregnancy unless the benefit outweighs the risk in very rare and special cases. If a woman needs anticoagulation and is planning to conceive or is pregnant, she should find an alternative anticoagulant such as a low-molecular-weight heparin (e.g., enoxaparin) or heparin (although with heparin, there may be a risk of osteoporosis with extended duration of use (Answer D is incorrect). A low-molecular-weight heparin would be the agent of choice (Answer C is correct).

4. Answer: D
Medroxyprogesterone acetate is added to conjugated estrogens to decrease the risk of endometrial cancer; venlafaxine is not relieving her hot flashes, therefore it should be discontinued (Answer D is correct). The addition of medroxyprogesterone acetate does not decrease the risk of stroke (Answer C is incorrect). Estrogen alone is insufficient because the patient has an intact uterus, as indicated by her medical history (no surgical procedures) (Answer A is incorrect). Venlafaxine is not relieving her hot flashes; therefore, it should be discontinued (Answer B is incorrect).

5. Answer: C
The patient is experiencing systemic symptoms such as hot flashes, and she has localized genitourinary atrophy, which probably results in pain during sexual intercourse. Estradiol vaginal cream and ospemifene are indicated for genitourinary atrophy, not for vasomotor symptoms (Answers A and D are incorrect). The best treatment would be an oral or transdermal systemic agent (Answer C is correct). The patient has had a hysterectomy; therefore, a progestogen in combination with estrogen is unnecessary (Answer B is incorrect).

6. Answer: C
The efficacy of lamotrigine may be decreased (Answer C is correct; Answer B is incorrect). Estrogen and drospirenone are not affected by lamotrigine (Answers A and D are incorrect). *(See Answer 6 table.)*

7. Answer: B
The number of patients needed to treat with valacyclovir over acyclovir to prevent one recurrent HSV genital infection (1 year of follow-up of study participants receiving suppressive therapy [acyclovir or valacyclovir], with 25% and 20%, respectively, experiencing a recurrent infection) is 20 = 1/(0.25−0.20) (Answer B is correct; all other answers are incorrect). The only information needed is the absolute risk in both groups (which is provided).

8. Answer: B
The patient has a history of migraine with aura, which precludes any estrogen product (oral ethinyl estradiol/desogestrel oral tablet and transdermal contraceptive patch). Her blood pressure is slightly elevated but not greater than 160/100 mm Hg, which would not be a contraindication for estrogen use; however, her migraine with aura rules out the use of estrogen products (Answers C and D are incorrect). She also has obesity at 215 lb (98 kg) and weighs more than 90 kg, so the patch is not recommended (again, Answer C is incorrect). The levonorgestrel IUS (Mirena, Kyleena, Skyla, Liletta) may be an option, but the patient is interested in conceiving in a year or so. Mirena and Kyleena, which work for up to 5 years, Skyla, which works for up for 3 years, and Liletta, which works for up to 5 years, would not be cost-effective for the patient (Answer A is incorrect). Norethindrone oral tablet is a progestogen-only pill and the best choice (Answer B is correct).

9. Answer: D
Serophene (clomiphene citrate) is the first-line choice to stimulate ovulation (Answer D is correct). Another first-line option could be an aromatase inhibitor such as letrozole; however, this was not an answer choice. Menopur (hMG), Synarel (GnRH agonist), and Ovidrel (hCG) are not first-line agents and are usually used after clomiphene citrate or aromatase inhibitors have failed or when the patient is undergoing assisted reproductive therapies (Answers A, B, and C are incorrect).

10. Answer: B
Clinical studies suggest that levonorgestrel emergency contraception is still effective for up to 120 hours after unprotected intercourse though package labeling only states 72 hours, and the patient does not need a prescription (Answer B is correct; Answer A is incorrect). She stated that her vaginal ring slipped out of place. If the vaginal ring had been out of place longer than 3 hours and unprotected intercourse had occurred, EC should have been recommended (Answers C and D are incorrect). When inserting a new vaginal ring, she should also be instructed to use a BUM for at least 7 days (again, Answer D is incorrect).

11. Answer: A
The patient's laboratory values are within normal limits, indicating that his disease states are not necessarily the cause of his erectile dysfunction. A phosphodiesterase inhibitor such as vardenafil may be initiated (Answer A is correct). Testosterone replacement would not be effective because the patient has normal testosterone concentrations (Answer B is incorrect). Yohimbine would not be considered first-line therapy because its efficacy is controversial (Answer C is incorrect). Fluoxetine is inappropriate because the patient does not have premature ejaculation (Answer D is incorrect).

12. Answer: B
Penicillin G 4 million units every 4 hours intravenously for 14 days after penicillin desensitization is the correct therapy for a patient with neurosyphilis who is allergic to penicillin (Answer B is correct). Levofloxacin would not cover syphilis (Answer A is incorrect). Three doses of benzathine penicillin G are indicated for late latent syphilis, not neurosyphilis (Answer C is incorrect). Furthermore, although azithromycin is an alternative for patients who are penicillin allergic in other situations, patients with neurosyphilis should be desensitized and given penicillin (Answer D is incorrect).

13. Answer: A
Data are continuous and probably normally distributed (given the large population of 360 patients in the study); therefore, a parametric test is indicated. Because ANOVA is a parametric test used to compare more than two groups, it would be appropriate (Answer A is correct). The Student t-test is a parametric test for comparing only two groups (Answer D is incorrect). A chi-square test is used to assess nominal data between two groups (Answer B is incorrect). The Mann-Whitney U test is a nonparametric analog to the Student t-test (Answer C is incorrect).

Answer 6 Table.*

Drugs Interfering with Oral Contraceptive Efficacy		Oral Contraceptives Interfering with the Efficacy of OtherDrugs	
Increased	**Decreased**	**Increased**	**Decreased**
Ascorbic acid	Anticonvulsants[a]	Benzodiazepines[b]	Benzodiazepines[c]
Acetaminophen-scheduled	Antibiotics	Theophylline and caffeine	Warfarin
Atorvastatin	Rifampin	Cyclosporine	Thyroid agents
Rosuvastatin	Theophylline	Corticosteroids	Hypoglycemics
Ginseng	St. John's wort	Alcohol	Methyldopa
NNRTIs[d]	NNRTI–nevirapine	β-Blockers	Metformin
Protease inhibitors[e]	Protease inhibitors[f]	Tricyclic antidepressants	Amprenavir
Tranexamic acid	Sulfonamides	Ropinirole	Lamotrigine
Voriconazole	Griseofulvin	Zolmitriptan	Fosamprenavir
	Bosentan		
	Tacrolimus		
	Modafinil		

Note. *Table not all-inclusive of all drug interactions; some interactions may exist that are not listed in this table.

[a]Barbiturates, phenytoin, primidone, carbamazepine, oxcarbazepine, felbamate, topiramate, vigabatrin

[b]Alprazolam, chlordiazepoxide, diazepam

[c]Temazepam

[d]Delavirdine, efavirenz

[e]Atazanavir, indinavir

[f]Nelfinavir, ritonavir, lopinavir/ritonavir, amprenavir

NNRTI = nonnucleoside reverse transcriptase inhibitor

Pediatrics

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Learning Objectives

1. Recommend therapeutic options to target the most common organisms in neonatal and pediatric sepsis and meningitis.
2. Identify the drugs available for preventing and treating respiratory syncytial virus and indications for use.
3. Explain the most common causative organisms of otitis media and potential treatment options.
4. Apply the recommended pediatric immunization schedule and discuss barriers to routine immunization.
5. Examine the differences in anticonvulsants, including pharmacokinetics and adverse effects, between children and adults.
6. Implement an appropriate treatment regimen for patients with attention-deficit/hyperactivity disorder.

Abbreviations in This Chapter:

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
ADHD	Attention-deficit/hyperactivity disorder
AOM	Acute otitis media
DTaP	Diphtheria, tetanus, and pertussis vaccine
FDA	U.S. Food and Drug Administration
HepB	Hepatitis B
IVIG	Intravenous immunoglobulin
LAIV	Live attenuated influenza vaccine
MMR	Measles, mumps, and rubella
OME	Otitis media with effusion
RSV	Respiratory syncytial virus
RV	Rotavirus
SCD	Sudden cardiac death
Tdap	Tetanus, diphtheria, and pertussis vaccine

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. A 15-year-old male adolescent with a medical history of exercise-induced asthma presents with fever, tachypnea, headache, photophobia, and myalgia. Which organism is most likely to be isolated from this patient?
   A. Respiratory syncytial virus (RSV).
   B. *Streptococcus pneumoniae.*
   C. Group B *Streptococcus.*
   D. *Pseudomonas aeruginosa.*

2. Which is the best assessment of the risk of severe RSV infection and subsequent need for prophylaxis in a 3-month-old girl born at 30 weeks' gestation?
   A. This patient should receive prophylaxis if she is 6 months or younger at the beginning of RSV season.
   B. This patient is at risk only if she has chronic lung disease (i.e., necessitating more than 21% oxygen for at least the first 28 days of life).
   C. All neonates born during RSV season should receive prophylaxis.
   D. This patient should receive prophylaxis only if she has additional risk factors, such as day care attendance or school-aged siblings.

3. Which statement about prophylaxis of bacterial meningitis is the most accurate?
   A. Close contacts of patients with pneumococcal meningitis should receive prophylaxis.
   B. Close contacts of patients with *Haemophilus influenzae* meningitis need prophylaxis only if their immunizations are not up to date.
   C. Rifampin is a first-line agent for prophylaxis against meningococcal meningitis.
   D. Prophylaxis against bacterial meningitis is no longer recommended regardless of the causative organism.

4. A 6-month-old infant who was born at 24 weeks' gestation is brought to the clinic in October for a routine checkup and immunizations. Which is the best recommendation to make for this patient's immunization schedule?
   A. Only two of the five immunizations due should be given at the same time; schedule another appointment for the next week to administer the rest.
   B. Oral polio vaccine should be used to reduce the number of injections needed to complete the schedule.

C. Vaccines should be based on his corrected gestational age rather than on his chronologic age because he was born prematurely.

D. Influenza vaccine should be administered with all other scheduled vaccinations.

5. A physician asks for your recommendation for treating a 5-year-old child with his first case of acute otitis media (AOM). Which statement is the best advice?

A. A blood culture should be obtained to identify the causative organism.

B. Antibiotics might not be warranted at this time.

C. Initiate azithromycin to treat atypical organisms (e.g., mycoplasma).

D. Administer intramuscular ceftriaxone.

6. A 16-year-old female adolescent with asthma, a history of ventricular septal defect, and attention-deficit/hyperactivity disorder (ADHD) was initially treated with methylphenidate immediate release, but her ADHD symptoms persisted at home and school. Her therapy was then changed to methylphenidate OROS (Concerta). The dose was maximized during the next several weeks; however, her symptoms were still not well controlled throughout the day. She and her family report adherence to the treatment regimen. Which is the best recommendation to make for treating her ADHD?

A. Switch to clonidine extended release.

B. Switch to extended-release mixed amphetamine salts (i.e., Adderall XR).

C. Switch to methylphenidate transdermal system (i.e., Daytrana).

D. Switch to atomoxetine.

7. A 7-year-old child with absence seizures is having breakthrough episodes on ethosuximide. Which is the most appropriate alternative therapy?

A. Valproic acid.

B. Phenytoin.

C. Phenobarbital.

D. Gabapentin.

8. In a retrospective study of the risk of appetite loss in adolescents taking a specific stimulant agent for ADHD management, 7 of 200 patients exposed to the stimulant showed appetite loss, compared with 1 of 198 control subjects (unexposed). Which choice best reflects the correct odds ratio of developing loss of appetite for the case subjects compared with the control subjects?

A. 3.

B. 6.

C. 7.

D. 8.

9. An investigator wants to establish a causal relationship between the use of ceftriaxone in premature neonates and the incidence of kernicterus. Which study design is best to use?

A. Case series.

B. Randomized controlled.

C. Retrospective cohort.

D. Crossover.

10. An 8-month-old infant born at 36 weeks' gestation with hypoplastic left heart disease is admitted during RSV season for stage II (of III) repair of his heart defect. Which statement is most accurate regarding the use of palivizumab for RSV prophylaxis in this patient?

A. He is not at significant risk of severe RSV infection; therefore, palivizumab is not indicated.

B. Palivizumab is indicated to reduce nosocomial transmission of RSV in high-risk patients.

C. Palivizumab is not indicated because he has undergone surgical repair of his heart defect.

D. A dose of palivizumab should be administered postoperatively and continued throughout the RSV season.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-Centered Pharmacotherapy
    a. Tasks 1, 2, 3, and 4
    b. Systems and Patient Care Problems
        i. Sepsis/Meningitis
        ii. Respiratory Syncytial Virus (RSV) Infection
        iii. Otitis media
        iv. Immunizations
        v. Pediatric Seizures
        vi. Attention-Deficit/Hyperactivity Disorder
2. Domain 2: Drug Information and Evidence-Based Medicine, Task 2

I. SEPSIS AND MENINGITIS

A. Clinical Presentation
1. Signs and symptoms
   a. Neonates (less than 28 days old or less than 44 weeks' corrected gestational age for premature neonates)
      i. General: Temperature instability, feeding intolerance, lethargy, grunting, nasal flaring, retractions, apnea
      ii. More likely to be associated with meningitis: Bulging fontanelle and seizures
   b. Infants (1–12 months) and children (1–18 years)
      i. General: Fever, loss of appetite, emesis, myalgias, arthralgias, cutaneous manifestations (e.g., petechiae, purpura, rash)
      ii. More likely to be associated with meningitis: Nuchal rigidity, back pain, Kernig sign (restriction in passive extension at the knee because of spasm of the hamstring muscles), Brudzinski sign (consists of reflex flexion of a lower extremity after passive flexion of the opposite extremity), headache, photophobia, altered mental status, and seizures
2. Early versus late onset neonatal sepsis
   a. Onset
      i. Early: Within 72 hours of birth
      ii. Late: After the first 72 hours of life
   b. Risk factors
      i. Early
         (a) Usually related to maternal or obstetric risk factors: very low birth weight (less than 1500 g), prolonged rupture of amniotic membranes (greater than 18 hours), maternal fever, prolonged labor, maternal genitourinary tract colonization with group B *Streptococcus*, maternal endometritis, or chorioamnionitis
      ii. Late
         (a) Unrelated to obstetric risk factors
         (b) Usually related to iatrogenic/nosocomial factors (e.g., endotracheal tubes, central venous catheters)
   c. Incidence
      i. Early
         (a) Incidence increases with decreasing gestational age:
            (1) 0.5 of 1000 live births (term neonates)
            (2) 1 of 1000 live births (late preterm neonates 34–36 weeks' gestation)
            (3) 6 of 1000 live births (preterm neonates less than 34 weeks' gestation)
            (4) 20 of 1000 live births (preterm neonates less than 29 weeks' gestation)
            (5) 32 of 1000 live births (preterm neonates 22–24 weeks' gestation)
         (b) Meningitis occurs in less than 10% of cases.
      ii. Late
         (a) Incidence increases with decreasing gestational age:
            (1) 9% greater than 34 weeks' gestation
            (2) 20% with very low birth weight less than 1500 g at birth
            (3) 56% 24–25 weeks' gestation
         (b) Meningitis occurs in 60% of cases

d. Mortality
    i. Increases with decreasing gestational age
        - 1.6% in term neonates
        - 30% in preterm neonates 25–28 weeks
        - 50% in preterm neonates 22–24 weeks

3. Definition of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock in children
    a. SIRS: Presence of at least two of the four following criteria, one of which must be abnormal temperature or leukocyte count:
        i. Core temperature greater than 38.5°C or less than 36°C
        ii. Tachycardia (value based on age) over a 1/2- to 4-hour period or for infants younger than 1 year: bradycardia (value based on age) over a 1/2-hour period
        iii. Tachypnea (value based on age)
        iv. Leukocyte count elevated or depressed for age or greater than 10% immature neutrophils
    b. Sepsis: SIRS in the presence of, or as a result of, suspected or proven infection
    c. Severe sepsis: Sepsis plus one of the following:
        i. Cardiovascular organ dysfunction
        ii. Acute respiratory distress syndrome
        iii. Two or more other organ dysfunctions
    d. Septic shock: Sepsis and cardiovascular organ dysfunction, defined as one of the following despite administration of a fluid bolus of 40 mL/kg or greater in 1 hour:
        i. Decrease in blood pressure less than 5th percentile on the basis of age or systolic blood pressure less than 2 SD on the basis of age
        ii. Need for vasoactive medications to maintain blood pressure
        iii. Two of the following:
            - Unexplained metabolic acidosis
            - Increased lactate
            - Oliguria (urinary output less than 0.5 mL/kg/hour)
            - Prolonged capillary refill greater than 5 seconds
            - Core to peripheral temperature gap greater than 3°C
4. Cerebrospinal fluid findings (Table 1)

Table 1. Cerebrospinal Fluid Findings

Laboratory Value	Normal Child	Normal Newborn	Bacterial Meningitis	Viral Meningitis
WBC (cells/mL)	0–6	0–30	>1000	100–500
Neutrophils (%)	0	2–3	>50	<40
Glucose (mg/dL)	40–80	32–121	<30	>30
Protein (mg/dL)	20–30	19–149	>100	50–100
RBC (cells/mL)	0–2	0–2	0–10	0–2

RBC = red blood cell count; WBC = white blood cell count.

Adapted with permission from the American Academy of Pediatrics: Wubbel L, McCracken GH. Management of bacterial meningitis: 1998. Pediatr Rev 1998;19:78-84.

Patient Case

1. An infant born at 36 weeks' gestation develops respiratory distress, hypotension, and mottling at 5 hours of life. The child is transported to the neonatal intensive care unit, where he has a witnessed seizure, and cultures are obtained. Maternal vaginal cultures are positive for group B *Streptococcus*, and three doses of penicillin were given to the mother before delivery. Which is the best empiric antibiotic regimen?

   A. Vancomycin plus cefotaxime.

   B. Ampicillin plus ceftazidime.

   C. Ampicillin plus ceftriaxone.

   D. Ceftazidime plus gentamicin.

B. Common Pathogens for Sepsis and Meningitis (Table 2)

Table 2. Common Pathogens

Age	Organism
0–1 mo	Early onset: Group B *Streptococcus* (*Streptococcus agalactiae*) – 40%–45% of cases in term and late-preterm neonates (20% of cases in preterm neonates < 34 weeks' gestation) *Escherichia coli* – 10%–15% of cases in term and late-preterm neonates (50% of cases in preterm neonates < 34 weeks' gestation) *Listeria monocytogenes* – < 2% of cases in term and late-preterm neonates Late onset: Viral (e.g., herpes simplex virus) Coagulase-negative *Staphylococcus* (nosocomial) Gram-negative bacteria (e.g., *Klebsiella* spp., *Pseudomonas* spp., *Enterobacter* spp.; nosocomial)
1–3 mo	Neonatal pathogens (see above), Group B *Streptococcus* - 39% of cases *Haemophilus influenzae* type B[a] *Neisseria meningitidis* - 12% of cases *Streptococcus pneumoniae* - 14% of cases
3 mo – 12 yr	*Haemophilus influenzae* type B[a] *Neisseria meningitidis* - 34%–55% of cases *Streptococcus pneumoniae* - 24%–45% of cases
> 12 yr	*Neisseria meningitidis* - 55% of cases *Streptococcus pneumoniae* - 21% of cases

[a]*H. influenzae* is no longer a common pathogen where the vaccine is routinely used.

C. Potential Empiric Antibiotic Regimens for Sepsis and Meningitis (Table 3)

Table 3. Potential Empiric Antibiotic Regimens

Age	Regimen
0–1 mo	Ampicillin + gentamicin[a]
1–3 mo	Ampicillin + ceftriaxone[b] or vancomycin[c] + ceftriaxone[b]
>3 mo	Ceftriaxone + vancomycin[c]

[a]May consider use of broader-spectrum gram-negative agents in very critically ill neonates depending on local antibiotic resistance data. Cefotaxime (or ceftazidime with cefotaxime drug shortage) may be considered instead of gentamicin when there is a concern for meningitis.

[b]May consider cefotaxime (or ceftazidime with cefotaxime drug shortage) instead of ceftriaxone for infants < 2 mo because of potential contraindications with ceftriaxone.

[c]May defer vancomycin if no concern for meningitis.

Patient Cases

2. Culture results for the patient in question 1 reveal gram-negative rods in the cerebrospinal fluid. Which recommendation regarding antibiotic prophylaxis is best?
   A. The patient's 5-month-old stepsister is at high risk because she is not fully immunized; therefore, the patient should receive rifampin.
   B. The patient should receive rifampin to eliminate nasal carriage of the pathogen.
   C. Antibiotic prophylaxis is not indicated in this case.
   D. All close contacts should receive rifampin for prophylaxis.

3. A 6-year-old boy presents to the emergency department with a temperature of 104°F (40°C), altered mental status, and petechiae. There is no history of trauma. The results of a toxicology screen are negative. A complete blood cell count reveals 32×10^3 cells/mm^3 with 20% bands. Culture results are pending. The patient has no known drug allergies. Which antibiotic regimen provides the best empiric coverage?
   A. Ampicillin plus gentamicin.
   B. Cefuroxime.
   C. Ceftriaxone plus vancomycin.
   D. Rifampin.

D. Sequelae of Meningitis
   1. Hearing loss
   2. Mental retardation and learning deficits
   3. Visual impairment
   4. Seizures
   5. Hydrocephalus
   6. Mortality 5%–10% (10%–20% in neonates)

E. Steroids for Meningitis
   1. Use of steroids for pediatric meningitis to prevent neurologic complications (e.g., hearing loss) is controversial.
   2 A large meta-analysis showed reduced hearing loss with *H. influenzae* type B (Hib) meningitis only in children. However, Hib is less common now with routine vaccination.
   3. Recommendations from the American Academy of Pediatrics (AAP) on this topic are summarized as follows:
      a. Dexamethasone may be considered for suspected bacterial meningitis caused by Hib in children older than 6 weeks after considering risk-benefit.
         i. Example: A child with signs/symptoms of meningitis has confirmed recent exposure to someone with a Hib infection
      b. Data are insufficient to recommend routine adjunctive corticosteroid therapy for pediatric pneumococcal meningitis.
      c. If dexamethasone is used, it should be administered before or at the same time as the first dose of antibiotics.
      d. The usual dosage is dexamethasone 0.15 mg/kg/dose every 6 hours for 2 days.

F. Chemoprophylaxis of Bacterial Meningitis
   1. Purpose: Prevent the spread of *H. influenzae* and *N. meningitidis*
   2. High-risk groups
      a. Household contacts
      b. Nursery or day care center contacts
      c. Direct contact (e.g., health care providers) with index patient's secretions during the 7 days preceding or up to 24 hours after initiation of appropriate antibiotic therapy
      d. Individuals with prolonged contact (more than 8 hours for N. meningitidis and 4 hours or more for H. influenzae) while close (less than 3 feet) to patient in the preceding 7 days of symptom onset
   3. Regimens (Table 4)

Table 4. Regimens for Chemoprophylaxis[a]

Drug	*Neisseria meningitidis*	*Haemophilus influenzae*
Rifampin	<1 mo old: 5 mg/kg/dose PO every 12 hr × 2 days ≥1 mo old: 10 mg/kg/dose (maximum 600 mg) PO every 12 hr × 2 days	<1 mo old: 10 mg/kg/dose PO daily × 4 days ≥ 1 mo old: 20 mg/kg/dose (maximum 600 mg) PO daily × 4 days
Ceftriaxone	<15 yr old: 125 mg IM × 1 dose ≥15 yr old: 250 mg IM × 1 dose	Not indicated
Ciprofloxacin[b]	≥1 mo old: 20 mg/kg/dose (maximum 500 mg) PO × 1 dose	

[a]Azithromycin is a possible alternative, but it is not routinely recommended.

[b]Ciprofloxacin should only be used if fluoroquinolone-resistant strains of *N. meningitidis* have not been reported in the community.

IM = intramuscularly; PO = orally/enterally.

II. RESPIRATORY SYNCYTIAL VIRUS INFECTION

A. Clinical Presentation
   1. Seasonal occurrence: Depends on geographic location and usually lasts 4–5 months
      a. Season onset ranges from October to late January
      b. Season offset ranges from late January to early April
      c. Exception: Florida has an earlier RSV season onset and longer duration than the rest of the country
   2. Signs and symptoms
      a. Neonates and infants: Lower respiratory tract symptoms (e.g., bronchiolitis and pneumonia), wheezing, lethargy, fever, irritability, poor feeding, and apnea
      b. Older children: Upper respiratory tract symptoms (e.g., rhinorrhea, cough)
      c. Most cases are mild and self-limited.
   3. RSV accounts for more than 80% of lower respiratory tract infections in infants younger than 1 year.
   4. RSV is the most common cause of pediatric bronchiolitis and pneumonia.

B. Risk Factors for Severe Disease
   1. Premature birth
   2. Chronic lung disease or bronchopulmonary dysplasia
   3. Cyanotic or complicated congenital heart disease
   4. Moderate to severe pulmonary hypertension
   5. Immunodeficiency
   6. Airway abnormalities or neuromuscular conditions compromising the handling of respiratory secretions
   7. Other
      a. Lower socioeconomic status
      b. Passive smoking
      c. Day care attendance
      d. Siblings younger than 5 years

Patient Case

4. You are screening infants during the current RSV season for risk factors associated with the development of severe RSV infection. Which patient is the best candidate for the use of palivizumab for RSV prophylaxis?

   A. An 18-month-old child, born at 26-weeks' gestation with a history of chronic lung disease who has not received oxygen or medications during the past 8 months.

   B. A 5-month-old infant, born at 28-weeks' gestation with a history of chronic lung disease who was discharged from the hospital without oxygen or medications.

   C. A 41-day-old infant, born at 31 weeks' gestation, without a history of chronic lung disease who will attend day care.

   D. A 10-month-old infant, born at 37 weeks' gestation, with a surgically repaired congenital heart defect.

C. Prophylaxis
   1. Nonpharmacologic: Avoid crowds during RSV season and conscientiously use good handwashing practice
   2. Palivizumab (Synagis®)
      a. Dosing: 15 mg/kg/dose intramuscularly, given monthly during RSV season for up to 5 doses
         i. There is a 58% decrease in palivizumab serum concentration after cardiopulmonary bypass; therefore, an additional postoperative dose of palivizumab is recommended as soon as the patient is medically stable.
      b. Effects on outcomes
         i. A 55% reduction in hospitalizations for RSV
         ii. No reduction in overall mortality
         iii. Does not interfere with the response to vaccines
         iv. Not recommended for the prevention of nosocomial transmission of RSV
      c. The AAP recommendations for use were most recently updated in 2014 and were reaffirmed in 2017 and again in 2019 (Table 5).

      Note that prophylaxis should be discontinued if an RSV hospitalization occurs.
   3. Other monoclonal antibodies and vaccines are in development; however, palivizumab is currently the only U.S. Food and Drug Administration (FDA)-approved product recommended for RSV prevention.

Table 5. AAP Guidelines for Palivizumab Use

Gestational Age (wk + days)	Age at Start of RSV Season (mo)	Other Required Criteria	Maximum Number of Doses
<29 + 0	<12	—	5
29 + 0 to 31+6	<12	Chronic lung disease necessitating more than 21% oxygen for at least the first 28 days of life	5
<32 + 0	<24	Consider prophylaxis for a second RSV season if chronic lung disease has necessitated medical therapy within the 6 months preceding the start of RSV season	5
Any	<12	Patient with hemodynamically significant acyanotic[a] congenital heart disease receiving medication for congestive heart failure *and* will need cardiac surgery	5
Any	<12	Moderate to severe pulmonary hypertension	5
Any	<12	Congenital abnormalities of airway or neuromuscular disease that impairs the ability to clear airway secretions	5
Any	<24	Profoundly immunocompromised (may be considered)	5

[a]Infants with cyanotic heart defects can be considered for prophylaxis after consultation with a pediatric cardiologist.

AAP = American Academy of Pediatrics; RSV = respiratory syncytial virus.

Patient Case

5. An 18-month-old infant with a history of premature birth and chronic lung disease is admitted to the pediatric intensive care unit with fever, respiratory distress necessitating intubation, and a 3-day history of coldlike symptoms. The results of a nasal swab are positive for RSV. Which is the best intervention?
   A. Palivizumab.
   B. Dexamethasone.
   C. Cefuroxime.
   D. Supportive care.

D. Treatment
   1. Supportive care
      a. Hydration
      b. Supplemental oxygen
      c. Mechanical ventilation as needed
      d. Analgesics for fever
   2. Ribavirin
      a. Active against RSV replication
      b. Not shown to reduce mortality in immunocompetent patients
      c. Not shown to reduce ventilator days, stay in the intensive care unit or hospital, or hospital cost
      d. The AAP states that oral ribavirin "may be considered" in a select group of high-risk patients (e.g., those with complicated congenital heart disease, chronic lung disease or bronchopulmonary dysplasia, immunocompromised) but that "routine use is not recommended."

3. Inhaled β_2-agonists, racemic epinephrine
    a. Not shown to improve outcome measures
    b. Some practitioners may give a trial of these therapies, but this is not considered the standard of care, nor is it recommended by the current AAP guideline.
4. Corticosteroids
    a. Not shown to improve outcome measures
    b. Use is not recommended.
5. Inhaled hypertonic saline
    a. Should not be administered in the emergency department
    b. May be considered for hospitalized patients; however, the evidence supporting use is weak.
6. Antibiotics: Not indicated unless secondary bacterial infection develops

III. OTITIS MEDIA

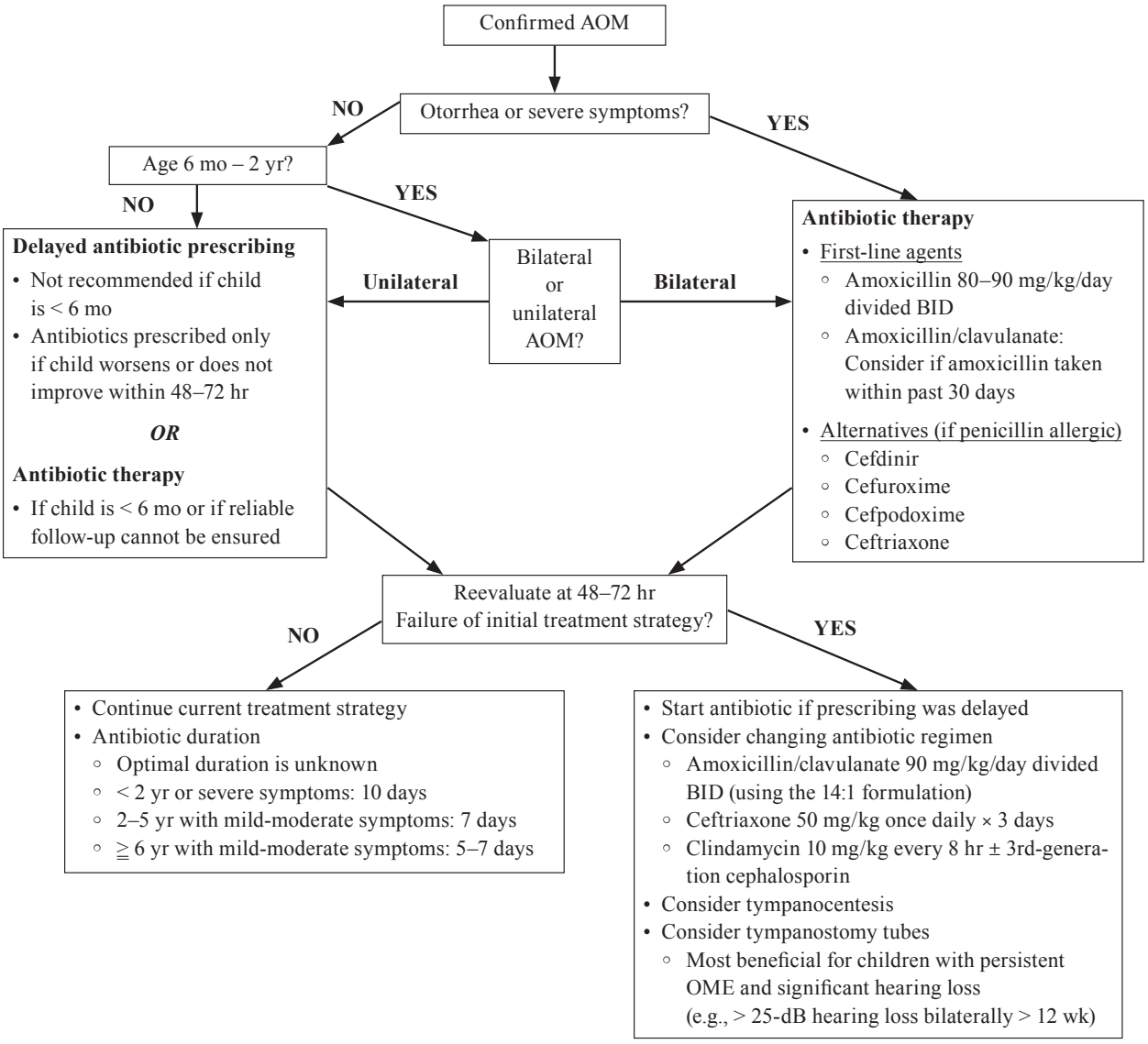
A. Clinical Presentation
    1. Definitions
        a. Acute otitis media: Presence of middle ear effusion and evidence of middle ear inflammation
            i. Middle ear effusion may be indicated by bulging tympanic membrane, decreased or no mobility of the tympanic membrane, purulent fluid in the middle ear.
            ii. Inflammation of the middle ear may be indicated by erythema of the tympanic membrane or otalgia.
        b. Otitis media with effusion (OME): Fluid in the middle ear without evidence of local or systemic illness
        c. Recurrent AOM: Three or more episodes of acute otitis within 6 months or four episodes within 1 year with at least 1 episode within the most recent 6 months
    2. Risk factors
        a. Younger age (generally less than school age)
        b. Day care attendance
        c. Absence of breastfeeding
        d. Family history of AOM
        e. Positioning during feeding (e.g., supine position during bottle-feeding allows reflux into Eustachian tubes)
        f. Lower socioeconomic status
        g. Smokers in the household
        h. Craniofacial abnormalities or cleft palate
        i. Lack of pneumococcal conjugate vaccine and influenza vaccine administration
        j. Immune deficiencies
        k. Cochlear implants
        l. Siblings in the home
        m. Seasonal cooler months (winter)
    3. Incidence
        a. AOM in first year of life: 25%
        b. AOM by 5 years of life: 60%
        c. Peak incidence at 6 to 12 months of age

B. Common Pathogens
   1. Viral
   2. *Streptococcus pneumoniae*
   3. Nontypeable *H. influenzae*
   4. *Moraxella catarrhalis*

C. Signs & Symptoms:
   1. Otorrhea
   2. Erythema
   3. Tugging or pulling of ears (otalgia)
   4. Fever
   5. Irritability/sleep changes

D. Treatment
   1. General principles
      a. Clinical resolution will occur in a significant number of cases without antibiotic therapy.
      b. Immediate antibiotic therapy is warranted for AOM with bulging tympanic membrane, perforation, or otorrhea.
      c. Delayed antibiotic prescribing (i.e., treatment only if symptoms are severe: otalgia persists for more than 48–72 hours or temperature greater than 102.2°F [39°C] in the past 48 hours) is an acceptable strategy in children older than 2 years with AOM without severe systemic symptoms.
         i. Analgesics (e.g., ibuprofen, acetaminophen) are more beneficial than antibiotics for relieving otalgia within the first 24 hours and are recommended regardless of antibiotic use.
            (a) Ibuprofen 5-10 mg/kg every 6-8 hours (not recommended if less than 6 months old)
            (b) Acetaminophen 10-15 mg/kg every 4-6 hours
         ii. Antibiotics also can be deferred in otherwise healthy children between 6 months and 2 years of age if their symptoms are mild and otitis media is unilateral (as opposed to bilateral).
         iii. Caregiver must be reliable to recognize worsening of condition and gain immediate access to medical care, if needed.
         iv. Not recommended for infants younger than 6 months
      d. Persistence of middle ear fluid is likely after treatment for AOM and does not warrant repeated treatment.
         i. 50% persistent OME after 1 month
         ii. 20% persistent OME after 2 months
         iii. 10% persistent OME after 3 months
      e. Antibiotics are not generally warranted for OME because of the high rate of spontaneous resolution.
         i. Antibiotics are recommended only if bilateral effusions persist for more than 3 months.
         ii. Corticosteroids, antihistamines, and decongestants are not recommended.

2. Suggested treatment algorithm (Figure 1)


Confirmed AOM
Otorrhea or severe symptoms?
NO
YES
Age 6 mo – 2 yr?
NO
YES
Delayed antibiotic prescribing
• Not recommended if child is < 6 mo
• Antibiotics prescribed only if child worsens or does not improve within 48–72 hr
OR
Antibiotic therapy
• If child is < 6 mo or if reliable follow-up cannot be ensured
Unilateral
Bilateral or unilateral AOM?
Bilateral
Antibiotic therapy
• First-line agents
◦ Amoxicillin 80–90 mg/kg/day divided BID
◦ Amoxicillin/clavulanate: Consider if amoxicillin taken within past 30 days
• Alternatives (if penicillin allergic)
◦ Cefdinir
◦ Cefuroxime
◦ Cefpodoxime
◦ Ceftriaxone
Reevaluate at 48–72 hr
Failure of initial treatment strategy?
NO
YES
• Continue current treatment strategy
• Antibiotic duration
◦ Optimal duration is unknown
◦ < 2 yr or severe symptoms: 10 days
◦ 2–5 yr with mild-moderate symptoms: 7 days
◦ ≧ 6 yr with mild-moderate symptoms: 5–7 days
• Start antibiotic if prescribing was delayed
• Consider changing antibiotic regimen
◦ Amoxicillin/clavulanate 90 mg/kg/day divided BID (using the 14:1 formulation)
◦ Ceftriaxone 50 mg/kg once daily × 3 days
◦ Clindamycin 10 mg/kg every 8 hr ± 3rd-generation cephalosporin
• Consider tympanocentesis
• Consider tympanostomy tubes
◦ Most beneficial for children with persistent OME and significant hearing loss (e.g., > 25-dB hearing loss bilaterally > 12 wk)

BID = twice daily; OME = Otitis media with effusion.

Figure 1. Suggested treatment algorithm for acute otitis media (AOM).

E. Complications of AOM: Incompletely treated or untreated:
   1. Hearing loss
   2. Mastoiditis
   3 Tympanic membrane perforation
   4. Otorrhea

F. Prevention Strategies
   1. Antibiotic prophylaxis
      a. Reduces occurrence by about one episode per year
      b. The risk of promoting bacterial resistance may outweigh the slight benefit.
      c. AAP recommends against routine use for children with recurrent AOM.
   2. Immunization: Pneumococcal and influenza vaccines should be administered according to the AAP and Advisory Committee on Immunization Practices (ACIP) recommendations.
   3. Modification of risk factors

Patient Cases

6. A 5-month-old infant who was born at term and is otherwise healthy was treated for her first case of otitis media with amoxicillin 45 mg/kg/day for 7 days. On follow-up examination, her pediatrician noticed fullness in the middle ear and a cloudy tympanic membrane with decreased mobility. She is now afebrile and eating well. Which is the best recommendation for her treatment?
   A. No antibiotics at this time.
   B. High-dose (90 mg/kg/day) amoxicillin for 7 days.
   C. Decongestant and antihistamine daily until resolution.
   D. Azithromycin.

7. A 4-year-old boy receives a diagnosis of his fourth case of otitis media within 12 months. He has not shown evidence of hearing loss or delay in language skills. Which is the best intervention at this point?
   A. Giving long-term antibiotic prophylaxis.
   B. Inserting tympanostomy tubes.
   C. Administering high-dose amoxicillin and ensuring that he is up to date on his pneumococcal and influenza vaccines.
   D. No antibiotic therapy is warranted.

IV. IMMUNIZATIONS

A. Recommended Schedule (Figure 2)
   1. Some major changes and several clarifications have been made to the routine childhood schedule in the last 10 years.
      a. Replacement of 7-valent conjugated pneumococcal vaccine with 13-valent conjugated pneumococcal vaccine (PCV13, Prevnar 13) for all children younger than 6 years
      b. Human papillomavirus vaccine (HPV4, Gardasil) received an FDA label-approved indication in males and females aged 9–26 years for prevention of genital warts and females aged 9–26 years for the prevention of cervical, vulvar, vaginal, and anal cancer. It is now recommended for routine vaccination of adolescent males and females.
      c. Live attenuated influenza vaccine (LAIV) was previously not recommended during the 2016-2017 and 2017-2018 influenza seasons. It was, however, considered an option again starting with the 2018-2019 season in patients to whom influenza injection would otherwise not be given. Use of LAIV must be assessed annually. LAIV should not be used in children younger than 2 years or children 2–4 years of age with a diagnosis of asthma in the preceding year. Caution should be used in children older than 5 years with asthma.

d. Hepatitis B (HepB) vaccine for the birth dose should be given within 24 hours of birth added to footnote of 2017 update.
e. For children and adolescents who have a delayed start to immunizations, a catch-up schedule exists.
f. A new figure for vaccines that might be indicated for children and adolescents aged 18 years or younger based on medical indications was added.
    i. Most children with medical conditions can (and should) be vaccinated according to the routine schedule.
    ii. It provides details for when a medical condition is a contraindication or precaution to vaccination.
    iii. It indicates when additional doses of vaccination may be required because of a medical condition.
g. Refer to the National Immunization Program Web site (www.cdc.gov/vaccines).
h. New formulations of licensed influenza vaccines with a volume of 0.5 mL per dose were approved for children 6–36 months of age in 2019. Children 6–35 months of age may now receive either the 0.25-mL or the 0.5-mL dose, with no preference, and children 36 months and older (3 years and older) continue to receive a 0.5-mL dose.

Patient Case

8. A 1-year-old boy with a history of Kawasaki disease treated 4 months ago with intravenous immunoglobulin (IVIG) is being seen by his pediatrician for a well-child checkup. He is due for the measles, mumps, and rubella (MMR) and varicella vaccines. He has no known drug allergies, but he has many food allergies, including peanuts and eggs. His mother has several concerns about administering these vaccines. Which concern is the best reason to defer administering vaccines in this patient?

    A. Association between MMR vaccine administration and the development of autism.
    B. Allergic reaction after MMR administration in a patient with an egg allergy.
    C. Many concurrent vaccines can overload the patient's immune system.
    D. Decreased vaccine efficacy because of previous IVIG administration.

2. Combination vaccines
    a. Main advantage: Reduction in the number of injections needed to complete recommended schedule
    b. The FDA mandates that the safety and efficacy of combination products not be less than those of the individual components.
    c. The MMR and varicella combination vaccine (ProQuad)
        i. Research from the Centers for Disease Control and Prevention and manufacturer indicated a higher incidence of febrile seizures in children 12–23 months of age who received the combination product compared with those who received the separate MMR and varicella vaccines.
        ii. Since June 2009, ACIP has expressed a preference for separate MMR and varicella vaccines as the first dose given to children 12–47 months of age. The combination product can be used for the second dose at any age and for the first dose in children age 48 months or older.
    d. Adding HepB to combination products can result in an extra dose being provided (e.g., monovalent HepB given at birth and then combination products at 2, 4, and 6 months); however, ACIP states that this is a safe practice.
3. Interchangeability of products
    a. ACIP recommends that the same product be used throughout the primary series; however, if the previous product's identity is not known or is no longer available, any product may be used.
    b. For diphtheria, tetanus, and pertussis vaccine (DTaP): The current standard of care is to use the same product for at least the first three doses of the five-dose series; however, if the product used previously is not known or is unavailable, any product can be used.

c. For tetanus, diphtheria, and pertussis vaccine (Tdap): Boostrix or Adacel can be used for the booster dose, regardless of the manufacturer of the DTaP product administered during the primary immunization series.
d. For HepB: It is acceptable to use Engerix-B and Recombivax HB interchangeably. Children and adolescents 11–15 years of age can receive a two-dose series with Recombivax HB only, whereas Engerix-B would still be a three-dose series. Heplisav-B should only be used in patients 18 years or older.
e. For polio: Oral polio vaccine and inactivated poliovirus vaccine provide equivalent protection against paralytic poliomyelitis; however, because the only cases of polio in the United States since 1979 have been vaccine associated (i.e., from the live virus in oral polio vaccine), oral polio vaccine is no longer recommended.
f. For Hib: These products can be used interchangeably; however, if the regimen is completed using PedvaxHIB exclusively, only three doses are needed for routine immunization; regimens using Hiberix, ActHIB, or Pentacel should include four doses even if the regimen is completed using PedvaxHIB.
g. For Rotavirus (RV): These products can be used interchangeably; however, if the regimen is completed using Rotarix exclusively, only two doses are needed; regimens using RotaTeq or when the product is unknown should include three doses.

B. Barriers to Routine Immunization
1. Contraindications
a. Anaphylactic reaction to vaccine or any of its components
i. Inactivated poliovirus vaccine, MMR, and varicella contain neomycin.
ii. Egg allergy is not considered a contraindication to any form of influenza vaccine. LAIV was approved for use in patients with egg allergy in 2016. Additionally, ACIP evaluated 3 studies looking at use of LAIV in egg-allergic children, and no cases of anaphylaxis occurred.
iii. Severe egg allergy is not considered a contraindication to MMR, which is grown in chick embryo tissue.
b. Acute moderate to severe febrile illness
c. Immunodeficiency: Oral polio vaccine, MMR, varicella
d. Pregnancy: MMR, varicella
e. Recent administration of immune globulin: MMR, varicella
i. Delay administration of vaccine product.
ii. Interval between immune globulin dose and administration of vaccine depends on indication for and dose of immune globulin.
f. Encephalopathy within 7 days after administration of a previous dose of DTaP
g. History of intussusception: Rotavirus vaccine
2. Misconceptions about contraindications (i.e., these are *not* contraindications)
a. Mild acute illness
b. Current antimicrobial therapy
c. Reaction to DTaP involving only soreness, redness, or swelling at the site
d. Pregnancy of the mother of the vaccine recipient
e. Breastfeeding
f. Allergies to antibiotics other than neomycin or streptomycin
g. Family history of an adverse effect after vaccine administration

3. Other factors associated with under-immunization
    a. Low socioeconomic status
    b. Late start of vaccination series
    c. Missed opportunities
        i. Provider unaware that vaccination is due
        ii. Failure to provide simultaneous vaccines
        iii. Inappropriate contraindications (see previous discussion)
    d. Concern about potential adverse reactions
        i. Autism: The association with MMR vaccine has not been proven.
        ii. Guillain-Barré syndrome: The association with meningococcal conjugate vaccine has not been proven.
            (a) Fifteen reported cases in adolescents after receiving meningococcal vaccine
            (b) ACIP continues to recommend the routine use of meningococcal vaccine.
        iii. Intussusception: An association with RV vaccine led to the market withdrawal of one particular brand of RV vaccine (RotaShield); two products are currently available.
            (a) Live, oral human-bovine reassortant rotavirus vaccine (RotaTeq, licensed in 2006)
            (b) Live, attenuated human rotavirus vaccine (Rotarix, licensed in 2008)
            (c) Neither product has been associated with intussusception.
        iv. Safety concerns about any vaccine product should be reported through the Vaccine Adverse Events Reporting System.
    e. Belief that vaccine-preventable diseases no longer pose a significant health risk
    f. Belief that too many vaccines all at once can overwhelm the immune system and make the child sick
    g. Religious or philosophical beliefs that oppose vaccinations

Patient Case

9. The following patients are seeing their pediatrician today and are due for immunizations according to the routine schedule. For which patient would it be best to recommend deferring immunizations until later?

    A. A 12-month-old boy who recently completed a cycle of chemotherapy for acute lymphocytic leukemia.

    B. A 6-month-old girl receiving amoxicillin for otitis media.

    C. A 12-month-old HIV-positive boy whose most recent CD4 count was greater than 1000.

    D. A 12-year-old girl completing a prednisone "burst" (1 mg/kg/day for 5 days) for asthma exacerbation.

C. Considerations in Special Populations (Figure 2)
    1. Preterm infants
        a. Immunize according to chronologic age, as opposed to corrected gestational age
        b. Do not lower vaccine doses
        c. If birth weight is less than 2 kg, delay HepB vaccine because of reduced immune response until the patient is 1 month old or at hospital discharge if it occurs before 1 month of age (unless the mother is positive for HepB surface antigen, in which case the newborn should receive HepB vaccine regardless of birth weight). Newborns to mothers with Hepatitis B should also receive Hepatitis B immune globulin.
    2. Children who are immunocompromised
        a. Should not receive live vaccines (e.g., MMR, varicella, rotavirus, LAIV, yellow fever, and oral typhoid)
        b. Inactivated vaccines and immune globulins are appropriate.
        c. Household contacts should not receive oral polio vaccine; however, MMR, influenza, varicella, and rotavirus vaccines are recommended.

3. Patients receiving corticosteroids
    a. Live vaccines can be administered to patients receiving the following:
        i. Topical corticosteroids
        ii. Physiologic maintenance doses
        iii. Low or moderate doses (less than 2 mg/kg/day of prednisone equivalent)
    b. Live vaccines can be given immediately after discontinuation of high doses (2 mg/kg/day or more of prednisone equivalent) of systemic steroids given for less than 14 days.
    c. Live vaccines should be delayed at least 1 month after discontinuing high doses (2 mg/kg/day or more of prednisone equivalent) of systemic steroids given for more than 14 days.
4. Patients with HIV infection
    a. MMR should be administered unless the patient is severely immunocompromised.
    b. Varicella should be considered for asymptomatic or mildly symptomatic patients.
    c. Inactivated vaccines should be administered routinely.

Table 1 Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2020

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars. To determine minimum intervals between doses, see the catch-up schedule (Table 2). School entry and adolescent vaccine age groups are shaded in gray.

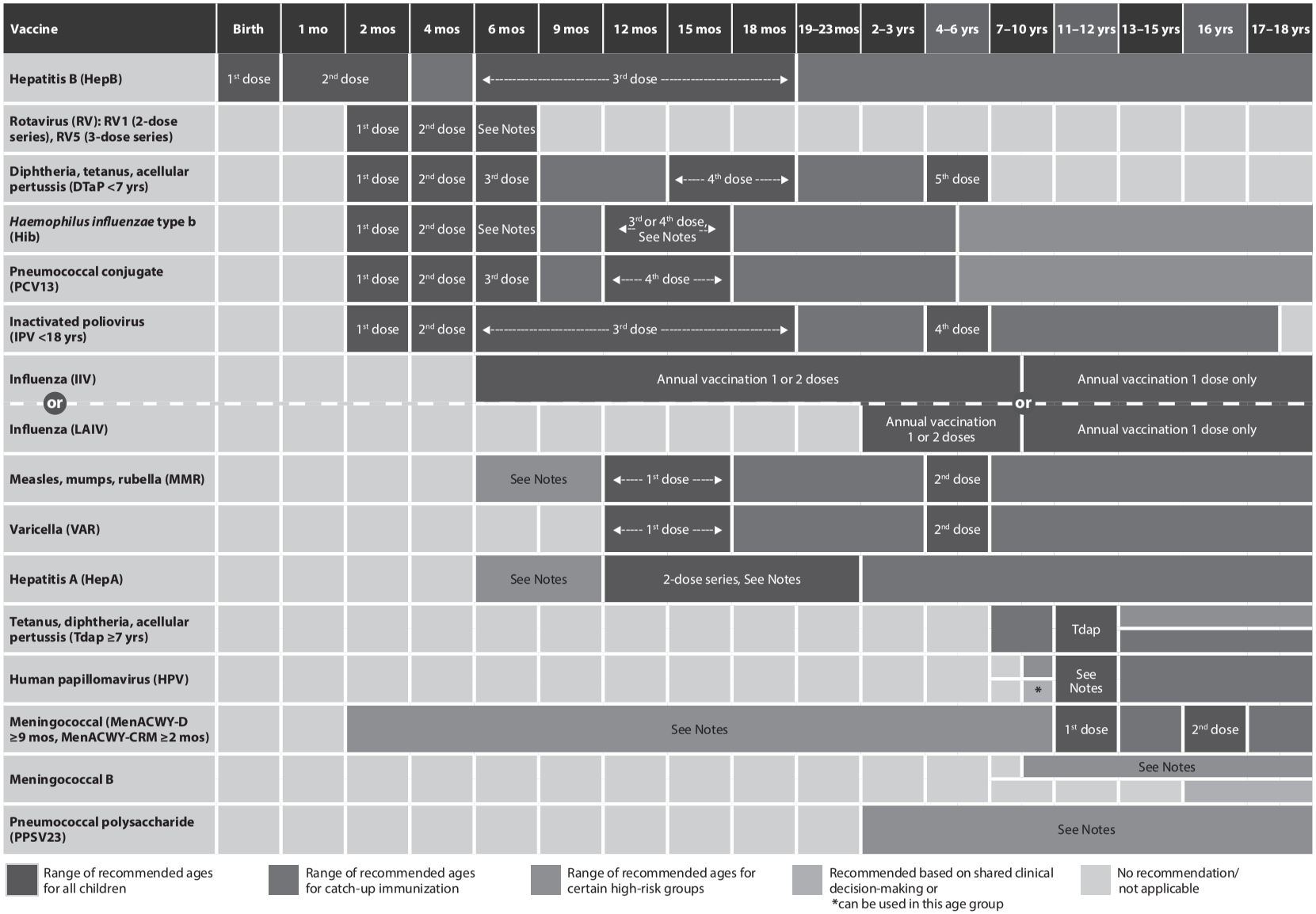


Figure 2. Recommended immunization schedule for children and adolescents 18 years or younger - United States, 2020. For those who fall behind or start late, see the catch-up schedule at https://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2020

For vaccine recommendations for persons 19 years of age or older, see the Recommended Adult Immunization Schedule.

Additional information

- Consult relevant ACIP statements for detailed recommendations at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For information on contraindications and precautions for the use of a vaccine, consult the General Best Practice Guidelines for Immunization at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html and relevant ACIP statements at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For calculating intervals between doses, 4 weeks = 28 days. Intervals of ≥4 months are determined by calendar months.
- Within a number range (e.g., 12–18), a dash (–) should be read as "through."
- Vaccine doses administered ≤4 days before the minimum age or interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum age or minimum interval should not be counted as valid and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see Table 3-1, Recommended and minimum ages and intervals between vaccine doses, in General Best Practice Guidelines for Immunization at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html.
- Information on travel vaccine requirements and recommendations is available at www.cdc.gov/travel/.
- For vaccination of persons with immunodeficiencies, see Table 8-1, Vaccination of persons with primary and secondary immunodeficiencies, in General Best Practice Guidelines for Immunization at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html, and Immunization in Special Clinical Circumstances (In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:67–111).
- For information regarding vaccination in the setting of a vaccine-preventable disease outbreak, contact your state or local health department.
- The National Vaccine Injury Compensation Program (VICP) is a no-fault alternative to the traditional legal system for resolving vaccine injury claims. All routine child and adolescent vaccines are covered by VICP except for pneumococcal polysaccharide vaccine (PPSV23). For more information, see www.hrsa.gov/vaccinecompensation/index.html.

Diphtheria, tetanus, and pertussis (DTaP) vaccination (minimum age: 6 weeks [4 years for Kinrix or Quadracel])

Routine vaccination

- 5-dose series at 2, 4, 6, 15–18 months, 4–6 years
  - **Prospectively:** Dose 4 may be administered as early as age 12 months if at least 6 months have elapsed since dose 3.
  - **Retrospectively:** A 4th dose that was inadvertently administered as early as 12 months may be counted if at least 4 months have elapsed since dose 3.

Catch-up vaccination

- Dose 5 is not necessary if dose 4 was administered at age 4 years or older and at least 6 months after dose 3.
- For other catch-up guidance, see Table 2.

Haemophilus influenzae type b vaccination (minimum age: 6 weeks)

Routine vaccination

- **ActHIB, Hiberix, or Pentacel:** 4-dose series at 2, 4, 6, 12–15 months
- **PedvaxHIB:** 3-dose series at 2, 4, 12–15 months

Catch-up vaccination

- **Dose 1 at 7–11 months:** Administer dose 2 at least 4 weeks later and dose 3 (final dose) at 12–15 months or 8 weeks after dose 2 (whichever is later).
- **Dose 1 at 12–14 months:** Administer dose 2 (final dose) at least 8 weeks after dose 1.
- **Dose 1 before 12 months and dose 2 before 15 months:** Administer dose 3 (final dose) 8 weeks after dose 2.
- **2 doses of PedvaxHIB before 12 months:** Administer dose 3 (final dose) at 12–59 months and at least 8 weeks after dose 2.
- **Unvaccinated at 15–59 months:** 1 dose
- **Previously unvaccinated children age 60 months or older** who are not considered high risk do not require catch-up vaccination.
- For other catch-up guidance, see Table 2.

Special situations

- **Chemotherapy or radiation treatment:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Doses administered within 14 days of starting therapy or during therapy should be repeated at least 3 months after therapy completion.
- **Hematopoietic stem cell transplant (HSCT):**
  - 3-dose series 4 weeks apart starting 6 to 12 months after successful transplant, regardless of Hib vaccination history
- **Anatomic or functional asplenia (including sickle cell disease):**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5 years or older*
  - 1 dose
- **Elective splenectomy:**
  Unvaccinated persons age 15 months or older*
  - 1 dose (preferably at least 14 days before procedure)
- **HIV infection:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5–18 years*
  - 1 dose
- **Immunoglobulin deficiency, early component complement deficiency:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

**Unvaccinated* = Less than routine series (through 14 months) OR no doses (15 months or older)

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2020

Hepatitis A vaccination
(minimum age: 12 months for routine vaccination)

Routine vaccination
- 2-dose series (minimum interval: 6 months) beginning at age 12 months

Catch-up vaccination
- Unvaccinated persons through 18 years should complete a 2-dose series (minimum interval: 6 months).
- Persons who previously received 1 dose at age 12 months or older should receive dose 2 at least 6 months after dose 1.
- Adolescents 18 years and older may receive the combined HepA and HepB vaccine, **Twinrix®**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (0, 7, and 21–30 days, followed by a dose at 12 months).

International travel
- Persons traveling to or working in countries with high or intermediate endemic hepatitis A (www.cdc.gov/travel/):
  - **Infants age 6–11 months**: 1 dose before departure; revaccinate with 2 doses, separated by at least 6 months, between 12 and 23 months of age
  - **Unvaccinated age 12 months and older**: Administer dose 1 as soon as travel is considered.

Hepatitis B vaccination
(minimum age: birth)

Birth dose (monovalent HepB vaccine only)
- **Mother is HBsAg-negative:** 1 dose within 24 hours of birth for **all** medically stable infants ≥2,000 grams. Infants <2,000 grams: Administer 1 dose at chronological age 1 month or hospital discharge.
- **Mother is HBsAg-positive:**
  - Administer **HepB vaccine** and **hepatitis B immune globulin (HBIG)** (in separate limbs) within 12 hours of birth, regardless of birth weight. For infants <2,000 grams, administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose.
- **Mother's HBsAg status is unknown:**
  - Administer **HepB vaccine** within 12 hours of birth, regardless of birth weight.
  - For infants <2,000 grams, administer **HBIG** in addition to HepB vaccine (in separate limbs) within 12 hours of birth. Administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Determine mother's HBsAg status as soon as possible. If mother is HBsAg-positive, administer **HBIG** to infants ≥2,000 grams as soon as possible, but no later than 7 days of age.

Routine series
- 3-dose series at 0, 1–2, 6–18 months (use monovalent HepB vaccine for doses administered before age 6 weeks)
- Infants who did not receive a birth dose should begin the series as soon as feasible (see Table 2).
- Administration of **4 doses** is permitted when a combination vaccine containing HepB is used after the birth dose.
- **Minimum age** for the final (3rd or 4th) dose: 24 weeks
- **Minimum intervals:** dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 8 weeks / dose 1 to dose 3: 16 weeks (when 4 doses are administered, substitute "dose 4" for "dose 3" in these calculations)

Catch-up vaccination
- Unvaccinated persons should complete a 3-dose series at 0, 1–2, 6 months.
- Adolescents age 11–15 years may use an alternative 2-dose schedule with at least 4 months between doses (adult formulation **Recombivax HB** only).
- Adolescents 18 years and older may receive a 2-dose series of HepB **(Heplisav-B®)** at least 4 weeks apart.
- Adolescents 18 years and older may receive the combined HepA and HepB vaccine, **Twinrix**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (0, 7, and 21–30 days, followed by a dose at 12 months).
- For other catch-up guidance, see Table 2.

Special situations
- Revaccination is not generally recommended for persons with a normal immune status who were vaccinated as infants, children, adolescents, or adults.
- **Revaccination** may be recommended for certain populations, including:
  - **Infants born to HBsAg-positive mothers**
  - **Hemodialysis patients**
  - **Other immunocompromised persons**
- For detailed revaccination recommendations, see www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepb.html.

Human papillomavirus vaccination
(minimum age: 9 years)

Routine and catch-up vaccination
- HPV vaccination routinely recommended at **age 11–12 years (can start at age 9 years)** and catch-up HPV vaccination recommended for all persons through age 18 years if not adequately vaccinated
- 2- or 3-dose series depending on age at initial vaccination:
  - **Age 9 through 14 years at initial vaccination**: 2-dose series at 0, 6–12 months (minimum interval: 5 months; repeat dose if administered too soon)
  - **Age 15 years or older at initial vaccination**: 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
- If completed valid vaccination series with any HPV vaccine, no additional doses needed

Special situations
- **Immunocompromising conditions, including HIV infection:** 3-dose series as above
- **History of sexual abuse or assault:** Start at age 9 years.
- **Pregnancy:** HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant; pregnancy testing not needed before vaccination

Influenza vaccination
(minimum age: 6 months [IIV], 2 years [LAIV], 18 years [recombinant influenza vaccine, RIV])

Routine vaccination
- Use any influenza vaccine appropriate for age and health status annually:
  - 2 doses, separated by at least 4 weeks, for **children age 6 months–8 years** who have received fewer than 2 influenza vaccine doses before July 1, 2019, or whose influenza vaccination history is unknown (administer dose 2 even if the child turns 9 between receipt of dose 1 and dose 2)
  - 1 dose for **children age 6 months–8 years** who have received at least 2 influenza vaccine doses before July 1, 2019
  - 1 dose for **all persons age 9 years and older**
- For the 2020–21 season, see the 2020–21 ACIP influenza vaccine recommendations.

Special situations
- **Egg allergy, hives only**: Any influenza vaccine appropriate for age and health status annually
- **Egg allergy with symptoms other than hives** (e.g., angioedema, respiratory distress, need for emergency medical services or epinephrine): Any influenza vaccine appropriate for age and health status annually in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions
- **LAIV should not be used** in persons with the following conditions or situations:
  - History of severe allergic reaction to a previous dose of any influenza vaccine or to any vaccine component (excluding egg, see details above)
  - Receiving aspirin or salicylate-containing medications
  - Age 2–4 years with history of asthma or wheezing
  - Immunocompromised due to any cause (including medications and HIV infection)
  - Anatomic or functional asplenia
  - Cochlear implant
  - Cerebrospinal fluid-oropharyngeal communication
  - Close contacts or caregivers of severely immunosuppressed persons who require a protected environment
  - Pregnancy
  - Received influenza antiviral medications within the previous 48 hours

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2020

Measles, mumps, and rubella vaccination (minimum age: 12 months for routine vaccination)

Routine vaccination
- 2-dose series at 12–15 months, 4–6 years
- Dose 2 may be administered as early as 4 weeks after dose 1.

Catch-up vaccination
- Unvaccinated children and adolescents: 2-dose series at least 4 weeks apart
- The maximum age for use of MMRV is 12 years.

Special situations
International travel
- **Infants age 6–11 months:** 1 dose before departure; revaccinate with 2-dose series with dose 1 at 12–15 months (12 months for children in high-risk areas) and dose 2 as early as 4 weeks later.
- **Unvaccinated children age 12 months and older:** 2-dose series at least 4 weeks apart before departure

Meningococcal serogroup A,C,W,Y vaccination (minimum age: 2 months [MenACWY-CRM, Menveo], 9 months [MenACWY-D, Menactra])

Routine vaccination
- 2-dose series at 11–12 years, 16 years

Catch-up vaccination
- Age 13–15 years: 1 dose now and booster at age 16–18 years (minimum interval: 8 weeks)
- Age 16–18 years: 1 dose

Special situations
Anatomic or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:
- **Menveo**
  - Dose 1 at age 8 weeks: 4-dose series at 2, 4, 6, 12 months
  - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart
- **Menactra**
  - **Persistent complement component deficiency or complement inhibitor use:**
    - Age 9–23 months: 2-dose series at least 12 weeks apart
    - Age 24 months or older: 2-dose series at least 8 weeks apart
  - **Anatomic or functional asplenia, sickle cell disease, or HIV infection:**
    - Age 9–23 months: Not recommended
    - Age 24 months or older: 2-dose series at least 8 weeks apart
    - **Menactra** must be administered at least 4 weeks after completion of PCV13 series.

Travel in countries with hyperendemic or epidemic meningococcal disease, including countries in the African meningitis belt or during the Hajj (www.cdc.gov/travel/)**:**
- Children less than age 24 months:
  - **Menveo (age 2–23 months):**
    - Dose 1 at 8 weeks: 4-dose series at 2, 4, 6, 12 months
    - Dose 1 at 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
  - **Menactra (age 9–23 months):**
    - 2-dose series (dose 2 at least 12 weeks after dose 1; dose 2 may be administered as early as 8 weeks after dose 1 in travelers)
- Children age 2 years or older: 1 dose **Menveo** or **Menactra**

First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) or military recruits:
- 1 dose **Menveo** or **Menactra**

Adolescent vaccination of children who received MenACWY prior to age 10 years:
- **Children for whom boosters are recommended** because of an ongoing increased risk of meningococcal disease (e.g., those with complement deficiency, HIV, or asplenia): Follow the booster schedule for persons at increased risk (see below).
- **Children for whom boosters are not recommended** (e.g., those who received a single dose for travel to a country where meningococcal disease is endemic): Administer MenACWY according to the recommended adolescent schedule with dose 1 at age 11–12 years and dose 2 at age 16 years.

Note: Menactra should be administered either before or at the same time as DTaP. For MenACWY **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting and for additional meningococcal vaccination information, see www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html.

Meningococcal serogroup B vaccination (minimum age: 10 years [MenB-4C, Bexsero; MenB-FHbp, Trumenba])

Shared clinical decision-making
- **Adolescents not at increased risk** age 16–23 years (preferred age 16–18 years) based on shared clinical decision-making:
  - **Bexsero:** 2-dose series at least 1 month apart
  - **Trumenba:** 2-dose series at least 6 months apart; if dose 2 is administered earlier than 6 months, administer a 3rd dose at least 4 months after dose 2.

Special situations
Anatomic or functional asplenia (including sickle cell disease), persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:
- **Bexsero:** 2-dose series at least 1 month apart
- **Trumenba:** 3-dose series at 0, 1–2, 6 months

Bexsero and **Trumenba** are not interchangeable; the same product should be used for all doses in a series.
For MenB **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting and for additional meningococcal vaccination information, see www.cdc.gov/vaccines/acip/recommendations.html and www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html.

Pneumococcal vaccination (minimum age: 6 weeks [PCV13], 2 years [PPSV23])

Routine vaccination with PCV13
- 4-dose series at 2, 4, 6, 12–15 months

Catch-up vaccination with PCV13
- 1 dose for healthy children age 24–59 months with any incomplete* PCV13 series
- For other catch-up guidance, see Table 2.

Special situations
High-risk conditions below: When both PCV13 and PPSV23 are indicated, administer PCV13 first. PCV13 and PPSV23 should not be administered during the same visit.

Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma treated with high-dose, oral corticosteroids), diabetes mellitus:

Age 2–5 years
- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Age 6–18 years
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Cerebrospinal fluid leak, cochlear implant:

Age 2–5 years
- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Age 6–18 years
- No history of either PCV13 or PPSV23: 1 dose PCV13, 1 dose PPSV23 at least 8 weeks later
- Any PCV13 but no PPSV23: 1 dose PPSV23 at least 8 weeks after the most recent dose of PCV13
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent dose of PPSV23

Notes

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Sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiency; HIV infection; chronic renal failure; nephrotic syndrome; malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and other diseases associated with treatment with immunosuppressive drugs or radiation therapy; solid organ transplantation; multiple myeloma:

Age 2–5 years
- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose) and a 2nd dose of PPSV23 5 years later

Age 6–18 years
- No history of either PCV13 or PPSV23: 1 dose PCV13, 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- Any PCV13 but no PPSV23: 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after the most recent dose of PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent PPSV23 dose and a 2nd dose of PPSV23 administered 5 years after dose 1 of PPSV23 and at least 8 weeks after a dose of PCV13

Chronic liver disease, alcoholism:

Age 6–18 years
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

**Incomplete series* = Not having received all doses in either the recommended series or an age-appropriate catch-up series See Tables 8, 9, and 11 in the ACIP pneumococcal vaccine recommendations at www.cdc.gov/mmwr/pdf/rr/rr5911.pdf for complete schedule details.

Poliovirus vaccination
(minimum age: 6 weeks)

Routine vaccination
- 4-dose series at ages 2, 4, 6–18 months, 4–6 years; administer the final dose at or after age 4 years and at least 6 months after the previous dose.
- 4 or more doses of IPV can be administered before age 4 years when a combination vaccine containing IPV is used. However, a dose is still recommended at or after age 4 years and at least 6 months after the previous dose.

Catch-up vaccination
- In the first 6 months of life, use minimum ages and intervals only for travel to a polio-endemic region or during an outbreak.
- IPV is not routinely recommended for U.S. residents 18 years and older.

Series containing oral polio vaccine (OPV), either mixed OPV-IPV or OPV-only series:
- Total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. See www.cdc.gov/mmwr/volumes/66/wr/mm6601a6.htm?s_cid=mm6601a6_w.
- Only trivalent OPV (tOPV) counts toward the U.S. vaccination requirements.
  - Doses of OPV administered before April 1, 2016, should be counted (unless specifically noted as administered during a campaign).
  - Doses of OPV administered on or after April 1, 2016, should not be counted.
  - For guidance to assess doses documented as "OPV," see www.cdc.gov/mmwr/volumes/66/wr/mm6606a7.htm?s_cid=mm6606a7_w.
- For other catch-up guidance, see Table 2.

Rotavirus vaccination
(minimum age: 6 weeks)

Routine vaccination
- **Rotarix:** 2-dose series at 2 and 4 months
- **RotaTeq:** 3-dose series at 2, 4, and 6 months
- If any dose in the series is either **RotaTeq** or unknown, default to 3-dose series.

Catch-up vaccination
- Do not start the series on or after age 15 weeks, 0 days.
- The maximum age for the final dose is 8 months, 0 days.
- For other catch-up guidance, see Table 2.

Tetanus, diphtheria, and pertussis (Tdap) vaccination
(minimum age: 11 years for routine vaccination, 7 years for catch-up vaccination)

Routine vaccination
- **Adolescents age 11–12 years:** 1 dose Tdap
- **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36
- Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine.

Catch-up vaccination
- **Adolescents age 13–18 years who have not received Tdap:** 1 dose Tdap, then Td or Tdap booster every 10 years
- **Persons age 7–18 years not fully vaccinated* with DTaP:** 1 dose Tdap as part of the catch-up series (preferably the first dose); if additional doses are needed, use Td or Tdap.
- **Tdap administered at 7–10 years:**
  - **Children age 7–9 years** who receive Tdap should receive the routine Tdap dose at age 11–12 years.
  - **Children age 10 years** who receive Tdap do not need to receive the routine Tdap dose at age 11–12 years.
- **DTaP inadvertently administered at or after age 7 years**:
  - **Children age 7–9 years**: DTaP may count as part of catch-up series. Routine Tdap dose at age 11–12 years should be administered.
  - **Children age 10–18 years**: Count dose of DTaP as the adolescent Tdap booster.
- For other catch-up guidance, see Table 2.
- For information on use of Tdap or Td as tetanus prophylaxis in wound management, see www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm.

**Fully vaccinated* = 5 valid doses of DTaP OR 4 valid doses of DTaP if dose 4 was administered at age 4 years or older

Varicella vaccination
(minimum age: 12 months)

Routine vaccination
- 2-dose series at 12–15 months, 4–6 years
- Dose 2 may be administered as early as 3 months after dose 1 (a dose administered after a 4-week interval may be counted).

Catch-up vaccination
- Ensure persons age 7–18 years without evidence of immunity (see www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have 2-dose series:
  - **Age 7–12 years**: routine interval: 3 months (a dose administered after a 4-week interval may be counted)
  - **Age 13 years and older**: routine interval: 4–8 weeks (minimum interval: 4 weeks)
  - The maximum age for use of MMRV is 12 years.

V. PEDIATRIC SEIZURE DISORDERS

A. Incidence of Pediatric Seizures
   1. Over 470,000 children in the United States with active epilepsy
   2 Highest incidence in infants and decreases to less than 1% of children aged 6-17 years old.
   3. Higher incidence with lower socioeconomic status and pre-existing developmental delays/disabilities
   4. Additional risk factors for seizures include trauma, infection, fever, metabolic imbalances, toxic ingestions, drug withdrawal, neurologic conditions, and medications

B. Febrile Seizures
   1. Febrile seizures are the most common seizure disorder in childhood
   2. Affects 2%–5% of children between the ages of 6 and 60 months
   3. Simple versus complex febrile seizures
      a. Simple: brief (less than 15 minutes) generalized seizures that occur once during a 24-hour period in a febrile child; no evidence of intracranial infection, metabolic disturbance, or history of febrile seizures
      b. Complex: one of the following in a febrile child
         i. Prolonged (more than 15 minutes) seizure
         ii. Focal seizure
         iii. Occur more than once in a 24-hour period
   4. Risk of developing epilepsy
      a. Children with simple febrile seizures have approximately the same risk of developing epilepsy as general population (about 1%)
      b. Higher risk if febrile seizures are recurrent, age younger than 12 months at time of first febrile seizure, or have a family history of epilepsy
   5. High rate of recurrence even for simple febrile seizure
      a. First simple febrile seizure at less than 12 months old: 50% probability of recurrence
      b. First simple febrile seizure at 12 months or older: 30% probability of recurrence
      c. Second simple febrile seizure: 50% probability of at least one recurrence
   6. Management of simple febrile seizures:
      a. Generally benign with excellent prognosis
      b. Risk of recurrence can be reduced with the following therapies; however, potential toxicities outweigh benefits, and these are not routinely recommended:
         i. Phenobarbital long-term therapy
         ii. Primidone long-term therapy
         iii. Valproic acid long-term therapy
         iv. Oral diazepam intermittent therapy for fevers
      c. Oral diazepam at fever recurrence can be considered when parental anxiety is severe
      d. Antipyretics are ineffective in preventing febrile seizures

C. Treatment Options Based on Seizure Type (Table 6)

Table 6. Treatment Options Based on Seizure Type

Seizure Type	Drugs of Choice	Alternatives
Neonatal	PB	LEV, PHT
Focal (formerly "partial")	CBZ, PHT, LTG, LEV, ZNS	PB, gabapentin, tiagabine, topiramate, oxcarbazepine, lacosamide, VPA[a]
Generalized		
Tonic-clonic	CBZ, PHT, LTG, LEV, ZNS	Topiramate, VPA[a]
Myoclonic	VPA[a], LEV	LTG, topiramate, ZNS, clobazam, rufinamide, felbamate
Absence	Ethosuximide, VPA[a]	Lamotrigine, ZNS
Lennox-Gastaut	VPA[a], topiramate, lamotrigine	Rufinamide, CBD, clobazam, felbamate, ZNS
Infantile spasms	ACTH injectable gel	Vigabatrin, lamotrigine, tiagabine, topiramate, VPA[a], ZNS

[a]Valproic acid can cause major congenital malformations and has a U.S. black box warning stating that it should not be administered to women of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable.

ACTH = adrenocorticotropic hormone; CBD = cannabidiol; CBZ = carbamazepine; LEV = levetiracetam, LTG = lamotrigine; PB = phenobarbital; PHT = phenytoin; VPA = valproic acid; ZNS = zonisamide.

D. Comparison of Available Antiseizure Drugs (Table 7)

Table 7. Comparison of Available Antiseizure Drugs

Drug	Adverse Effects	Pharmacokinetic Considerations	Other Comments
Brivaracetam	Dizziness Sleepiness Nausea and vomiting Behavioral reactions	Substrate of CYP2C19	Poor metabolizers of CYP2C19 may require dose reduction FDA-approved medication guide must be dispensed with medication
Cannabidiol	Somnolence/fatigue Increased liver enzymes Hypersensitivity reactions Decreased appetite and weight loss Diarrhea Insomnia	Moderate inhibitor of CYP2C19 High-fat/high-calorie meals increase extent of absorption	Schedule C-V Sugar-free oral solution
Carbamazepine	Rash (Black Box Warning) Hyponatremia ↓ Bone density Teratogenic DRESS syndrome Bone marrow suppression	Autoinduction ↓ Effectiveness of OCs Major CYP3A4 substrate	Significant drug interactions Routine therapeutic drug monitoring NIOSH hazardous drug HLA-B*1502 associated with SJS/TEN
Clobazam	Somnolence	Dose adjustment needed in hepatic impairment Dose adjustment needed in CYP2C19 poor metabolizers Long half-life	Long-acting benzodiazpine Tolerance may develop over time
Eslicarbazepine	Dizziness Nausea Diplopia	Substrate of UGT2B4 Moderate inducer of CYP3A4 Dose adjustment needed with renal impairment. Avoid use in severe hepatic impairment.	Significant drug interactions NIOSH hazardous drug

Table 7. Comparison of Available Antiseizure Drugs *(Cont'd)*

Drug	Adverse Effects	Pharmacokinetic Considerations	Other Comments
Ethosuximide	Abdominal pain, anorexia, diarrhea Drowsiness	Substrate of CYP3A4	Ineffective for seizure types other than absence
Felbamate	Anorexia, nausea, weight loss Insomnia, somnolence Aplastic anemia Hepatic failure	Clearance approximately 50:50 renal/hepatic	Significant drug interactions Aplastic anemia: Adults > children Requires signed informed consent
Gabapentin	Somnolence Weight gain	↑ Clearance in children < 6 yr Dose adjustment needed in renal insufficiency (no specific recommendations/studies for < 12 years old) Nonlinear pharmacokinetics	Minimal drug interactions Minimal cognitive effects May worsen Lennox-Gastaut
Lacosamide	Prolonged PR interval Dizziness Headache Diplopia	Dose adjustment needed in severe renal insufficiency	Use with caution if severe cardiac disease or conduction problems; caution with beta-blockers and some Ca channel blockers because of potential prolonged PR interval, AV block, or bradycardia No other clinically significant drug interactions
Lamotrigine	Rash/SJS/DRESS syndrome (Black Box Warning)	Autoinduction	Rash: Children > adults Minimal cognitive effects NIOSH hazardous drug
Levetiracetam	Headache Somnolence Behavioral changes	Renal excretion Clearance 40% ↑ in children No effect on CYP system	Minimal drug interactions Behavioral effects (e.g., aggression, agitation, mood changes): children > adults
Oxcarbazepine	Hyponatremia (> CBZ) Rash (< CBZ)	Clearance 40% ↑ in children < 6 yr Induces CYP3A4 Inhibits CYP2C19 ↓ Effectiveness of OCs	Hyponatremia: adults > children Minimal cognitive effects NIOSH hazadous drug
Perampanel	Dizziness Nausea Somnolence Fatigue Irritability Headache	Substrate of CYP3A4 Minor substrate of CYP1A2 and CYP2B6	Black box warning for neuropsychiatric events
Phenobarbital	Cognitive dysfunction Sedation Rash ↓ Bone density DRESS syndrome	High Protein Binding ↓ Effectiveness of OCs Autoinduction Long half-life	Significant drug interactions Routine therapeutic drug monitoring

Table 7. Comparison of Available Antiseizure Drugs *(Cont'd)*

Drug	Adverse Effects	Pharmacokinetic Considerations	Other Comments
Phenytoin and Fosphenytoin	Rash Gingival hyperplasia Hirsutism ↓ Bone density Teratogenic Phlebitis and extravasation DRESS syndrome Arrhythmias	Nonlinear pharmacokinetics ↓ Effectiveness of OCs	Significant drug interactions NIOSH hazardous drug Reduced risk of extravasation and hypotension with fosphenytoin Routine therapeutic drug monitoring HLA B*1502 associated w/increased risk of SJS/TEN Shake well before use Adheres to feeding tubes
Pregabalin	Somnolence Behavioral problems Dizziness Weight gain Ataxia Angioedema	AUC is ~30% lower while fasting	Minimal drug interactions
Rufinamide	Somnolence Rash QT interval shortening	↑ Level with concurrent VPA	Somnolence: Minimized with slow dose titration Rash: All reported cases are in children Administer with food
Stiripentol	Appetite/weight loss Drowsiness/dizziness Neutropenia Thrombocytopenia	↓ Clearance with increasing body weight (adolescents may require lower dosing than younger children) Valproate dose reduction by 30% may help minimize appetite/weight loss Systemic exposure is slightly higher with the powder for suspension than with capsules	Not approved for use as monotherapy. Should be used with clobazam (labeled use) or valproate (off-label) Approved for use in Dravet syndrome
Tiagabine	Dizziness Nonconvulsive status epilepticus (case reports)	Clearance 50% ↑ in children	Minimal cognitive effects
Topiramate	Cognitive dysfunction Weight loss Glaucoma Oligohidrosis Metabolic acidosis Nephrolithiasis	↑ Clearance in children Dose adjustment needed in renal insufficiency	Weight loss more common in obese patients Children at higher risk of oligohidrosis than adults NIOSH hazardous drug
Valproic acid	Weight gain Menstrual irregularities Polycystic ovarian syndrome Hyperandrogenism Hepatotoxicity (Black Box Warning) Teratogenic (Black Box Warning) Thrombocytopenia Pancreatitis (Black Box Warning)	CYP induction > in children	Significant drug interactions; Most cases of hepatotoxicity in children < 2 yr old (often if multiple AEDs) NIOSH hazardous drug Routine therapeutic drug monitoring Use sprinkles (opened caps) on food for ease of administration in small children

Table 7. Comparison of Available Antiseizure Drugs *(Cont'd)*

Drug	Adverse Effects	Pharmacokinetic Considerations	Other Comments
Vigabatrin	Vision loss (Black Box Warning) Weight gain		Available only through restricted distribution program NIOSH hazardous drug
Zonisamide	Weight loss Rash Oligohidrosis Somnolence Agitation Hallucinations Metabolic acidosis Nephrolithiasis	Primarily renal excretion No effect on CYP system	Better tolerated by children than by adults NIOSH hazardous drug

CBZ = carbamazepine; CYP = cytochrome P450; DRESS = drug reaction with eosinophilia and systemic symptoms; NIOSH = National Institute for Occupational Safety and Health; OC = oral contraceptive; PHT = phenytoin; SJS = Stevens-Johnson Syndrome; TEN = toxic epidermal necrolysis; VPA = valproic acid; ↓ = decreased; ↑ = increased.

Patient Case

10. A 14-year-old female adolescent with moderate obesity comes to the clinic with an erythematous pruritic rash. She was given oxcarbazepine about 3 weeks ago for the management of focal seizures. Her medical history is significant only for seizures. She recently became sexually active with a male and admits inconsistent contraceptive use. Which intervention is best for her?

    A. Change to carbamazepine.

    B. Change to levetiracetam.

    C. Change to valproic acid.

    D. No change in therapy is necessary.

VI. ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

A. Clinical Presentation
   1. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* criteria
      a. Either (i) or (ii) or combined presentation when all core features present
         i. Six or more (five or more if 17 years or older) of the following symptoms of inattention have been present for at least 6 months to a point that is disruptive and inappropriate:
            (a) Often does not give close attention to detail; makes careless mistakes
            (b) Often has trouble keeping attention on tasks and activities
            (c) Often does not seem to listen
            (d) Often does not follow instructions
            (e) Often has trouble organizing activities
            (f) Often avoids or dislikes things that require long periods of mental effort
            (g) Often loses things needed for tasks or activities
            (h) Often is easily distracted
            (i) Often is forgetful

ii. Six or more of the following symptoms of hyperactivity-impulsivity have been present for at least 6 months to a point that is disruptive and inappropriate:
(a) Hyperactivity
(1) Often fidgets or squirms
(2) Often is unable to remain seated when it is expected
(3) Often runs or climbs when and where it is not appropriate
(4) Often has difficulty with quiet play or activities
(5) Often is "on the go"
(6) Often talks excessively
(b) Impulsivity
(1) Often blurts out answers
(2) Often has difficulty waiting one's turn
(3) Often interrupts

b. Some symptoms were present by 12 years of age.
c. Some impairment from the symptoms is present in two or more settings.
d. Clear evidence of significant impairment exists in social, school, or work functioning.
e. No other mental disorder better describes the symptoms.

2. Comorbid disease states: 44%–87% of children with ADHD have at least one other disorder
a. Oppositional defiant disorder
i. Most common comorbid disorder in adolescents
ii. Presence of ADHD increases the odds of oppositional defiant disorder almost 11-fold.
b. Anxiety disorder: May exist in about 25% of children with ADHD
c. Tics
i. 21%–90% of children with Tourette syndrome may also have ADHD.
ii. May not be exacerbated by stimulant agents, as once thought

Patient Case

11. A 9-year-old boy has a new diagnosis of ADHD. At school, he is disruptive, talks when the teacher is talking, and runs around the classroom. His parents report extreme difficulty in getting him to do his homework after school. Which is best for his initial drug therapy?

A. Methylphenidate OROS (Concerta) given once daily.
B. Methylphenidate immediate release (Ritalin) given twice daily, with doses administered 4 hours apart.
C. Guanfacine given at bedtime.
D. D-Methylphenidate (Focalin) given twice daily, with doses administered 4 hours apart.

B. Classification: Based on *DSM-5* Criteria
1. ADHD, combined type: Criteria (i) and (ii) both are met.
2. ADHD, predominantly inattentive type: Criterion (i) is met, but (ii) is not met.
3. ADHD, predominantly hyperactive-impulsive type: Criterion (ii) is met, but (i) is not met.

C. Treatment Options: Combination of pharmacotherapy and behavioral therapy is more beneficial than either intervention alone.
   1. Factors affecting choice of pharmacologic agent
      a. Desired length of coverage time for symptoms
         i. Consider time of day when symptoms occur.
         ii. Consider time of day when child's activities occur (e.g., when is homework done, at what time are teenagers driving, when is child's bedtime).
      b. Child's ability to swallow pills or capsules
      c. Concomitant disease states (e.g., tic disorders)
      d. Adverse effect profile
      e. Concerns about abuse or diversion potential
         i. Children with ADHD are more likely to have a concurrent substance use disorder than those without ADHD.
         ii. Treatment with stimulant medication can reduce the risk of developing a substance use disorder.
         iii. Children treated with stimulants at a younger age are less likely to misuse or abuse substances than those in whom treatment is delayed.
      f. Expense
   2. Available pharmacologic agents
      a. Stimulant medications: Highly effective for most children in reducing core symptoms of ADHD. Some children with ADHD respond better to one stimulant type than another; therefore, both methylphenidate- and amphetamine-containing products should be tried before stimulant treatment is deemed a failure.
         i. Methylphenidate-containing products
            (a) Ramp effect: Behavioral effects are proportional to the rate of methylphenidate absorption into the central nervous system.
            (b) See Table 8 for a comparison of available products.
            (c) Adverse effects and precautions
               (1) Headache, stomachache, loss of appetite, and insomnia
               (2) Use with caution in patients with glaucoma, tics, psychosis, and concomitant monoamine oxidase inhibitor use.
               (3) Insomnia, anorexia, and tics occur more often with transdermal patch; also mild skin reactions.
         ii. Amphetamine-containing products
            (a) See Table 8 for a comparison of available products.
            (b) Adverse effects and precautions
               (1) Loss of appetite, insomnia, abdominal pain, and nervousness
               (2) Can exacerbate preexisting hypertension and tic disorders
               (3) Labeling change warns of potential association with sudden cardiac death (SCD); therefore, these are not recommended for patients with known structural heart defects.
         iii. Potential association with SCD
            (a) No established evidence of causative relationship between stimulants and SCD
            (b) The frequency of SCD is no higher in children taking stimulants than in the general pediatric population.
            (c) The AAP recommends targeted cardiac history and careful physical examination before initiating stimulant therapy.
               (1) Routine electrocardiography is not recommended unless history and physical examination suggest cardiac disease.
               (2) For otherwise healthy children, stimulant therapy should not be withheld because of the inability to obtain an electrocardiogram or assessment by a pediatric cardiologist.

b. Non-stimulant medications: Demonstrated efficacy in reducing core symptoms of ADHD; however, less evidence to date compared with stimulant medications.
    i. Norepinephrine reuptake inhibitors (see Table 9): FDA-approved for the treatment of ADHD
        (a) Adverse effects: Dyspepsia, decreased appetite, weight loss, and fatigue
        (b) Labeling change warns of potential for severe liver injury, although routine monitoring of hepatic function is not necessary.
        (c) Black box warning about increased risk of suicidal ideation in children and adolescents
        (d) Does not exacerbate tics
    ii. α-Adrenergic receptor agonists (see Table 9): FDA-approved for the treatment of ADHD
    iii. Antidepressants: Non-FDA label approved for the treatment of ADHD
        (a) Noradrenergic antidepressant (e.g., bupropion [Wellbutrin])
            (1) Can use immediate- or extended-release product given in two or three doses
            (2) Contraindicated for children with active seizure disorder
        (b) Tricyclic antidepressants (e.g., imipramine, nortriptyline)
            (1) Baseline electrocardiogram is recommended before therapy initiation and after each dose increase.
            (2) Desipramine should be used with extreme caution because of reports of sudden death.

3. AAP recommendations for treatment
    a. Children 4-5 years old:
        i. Behavior therapy as first-line treatment
        ii. Methylphenidate as second-line treatment
    b. Children 6-11 years old:
        i. Medication and behavioral therapy as first-line treatment
            (a) Stimulants have better evidence
            (b) Non-stimulants may be considered but evidence is weaker
    c. Adolescents 12-18 years old:
        i. Medication (with assent of child) as first-line treatment
            (a) Any FDA-approved medication
        ii. May also consider behavioral treatment

Table 8. Stimulant Agents for the Treatment of ADHD

Medication	Doses per Day	Onset of Effect	Duration of Effect (hr)	Other Comments
Methylphenidate-Containing Products				
Methylphenidate immediate release (Ritalin, Methylin chewable tablets, Methylin oral solution)	2 or 3	20–60 min	3–5	50:50 racemic mixture of l-threo and d-threo isomers
Dexmethylphenidate (Focalin)	2 or 3	20–60 min	3–5	Only D-threo isomer, thought to be pharmacologically active enantiomer D-Threo isomer has not been shown to hinder effectiveness or increase adverse effects Recommended doses are half those of methylphenidate immediate release Offers no proven pharmacoeconomic benefit over methylphenidate immediate-release products
Methylphenidate sustained release (Ritalin SR)	1 or 2	1–3 hr	2–6	
Methylphenidate extended release (Ritalin LA)	1	20–60 min	6–8	Contains 50% immediate-release and 50% extended release beads Capsule may be opened and sprinkled on applesauce Efficacy may wane in after-school or late-afternoon hours, necessitating addition of methylphenidate immediate release for later-day coverage
Methylphenidate modified release (Metadate CD)	1	20–60 min	6–8	Capsule contains 30% immediate-release and 70% extended-release beads (slowly released about 4 hr after ingestion) Capsule may be opened and sprinkled on applesauce Efficacy may wane in after-school or late afternoon hours, necessitating addition of methylphenidate immediate release for later-day coverage
Methylphenidate extended release chewable tablet (QuilliChew ER)	1	45 min	8	Alcohol concentration of 40% resulted in 90% of the methylphenidate being released in the first hour; avoid consuming alcohol during therapy.
Dexmethylphenidate extended release (Focalin XR)	1	20–60 min	8–12	Bimodal drug release results in peak serum concentrations at 1½ and 6½ hr after dose administration Shorter duration of action than methylphenidate OROS, so afternoon symptom control is not as good
Methylphenidate extended release (Metadate ER, Relexxii)	1	60 min	12	
Methylphenidate OROS (Concerta)	1	20–60 min	12	Outer capsule contains about 22% of the drug, allowing immediate release; tablet core contains remainder of drug, which is released over 10 hr, minimizing peak to trough fluctuations Swallow whole; *do not* chew, crush, or divide
Methylphenidate orally disintegrating tablet (Cotempla XR-ODT)	1	60 min	12	Contains 25% IR and 75% ER methylphenidate. Tablet should remain in blister pack until ready to use. Do not crush or chew. Place on tongue to disintegrate.

Table 8. Stimulant Agents for the Treatment of ADHD *(Cont'd)*

Medication	Doses per Day	Onset of Effect	Duration of Effect (hr)	Other Comments
Methylphenidate-Containing Products				
Methylphenidate transdermal system (Daytrana)	1	60 min	11–12	Apply to hip 2 hr before effect is needed Recommended to remove 9 hr after application; can be worn up to 16 hr Duration of effect is about 3 hr after patch removal Can be worn while swimming or exercising
Methylphenidate reconstituted oral suspension (Quillivant XR)	1	45 min	12	Contains sodium benzoate. Banana flavor. Store reconstituted suspension in original container for up to 4 months. Shake bottle ≥10 seconds prior to administration. Use the oral dosing dispenser provided. Once reconstituted with water forms an extended release suspension that contains approximately 20% immediate release and 80% extended release methylphenidate.
Methylphenidate extended release (Aptensio XR, Adhansia XR, Jornay PM)	1	2 hr	12	Contains multi layered beads.
Amphetamine-Containing Products				
Mixed amphetamine salts immediate release (Adderall)	1-3	20–60 min	6	
Amphetamine/ dextroamphetamine tablets (Evekeo)	1-3	45 min	6	Contains d-amphetamine and l-amphetamine in a 1:1 ratio.
Dextroamphetamine oral solution (ProCentra)	1-3	60 min	4-6	Bubblegum flavor. Shake suspension well before administration.
Dextroamphetamine immediate-release tablets (Zenzedi)	1–2	30–90 min	4–6	
Dextroamphetamine extended release capsule (Dexedrine spansules)	1-2	60-90 min	6-8	Bead-filled capsule (50% released immediately, 50% delayed release)
Mixed amphetamine salts extended release (Adderall XR)	1	20–60 min	10-12	Contains 50% immediate-release and 50% extended release beads (released 4 hr after ingestion) Can be sprinkled on applesauce
Amphetamine extended release oral suspension (Dyanavel XR, Adzenys ER)	1	60 min	12	Contains d-amphetamine and l-amphetamine in a 3:1 ratio. Shake bottle before use
Amphetamine extended release oral disintegrating tablets (Adzenys XR-ODT)	1	20-60 min	10-12	Store in travel case provided.
Lisdexamfetamine dimesylate (Vyvanse)	1	60 min	10–12	Prodrug with D-amphetamine covalently bound to L-lysine Designed for less abuse potential than amphetamine No clinical evidence of superiority over other amphetamine products
Mixed amphetamine salts extended release (Mydayis)	1	2-4 hr	16	Administer immediately after waking due to long duration. May open capsule and sprinkle contents on food.

ADHD = attention-deficit/hyperactivity disorder.

Table 9. Non-stimulant Agents for the Treatment of ADHD

Medication	Doses per Day	Onset of Effect (wk)	Duration of Effect (hr)	Other Comments
Norepinephrine Reuptake Inhibitor				
Atomoxetine (Strattera)	1 or 2	2–4	10–12	Can be considered first-line therapy for children with active substance abuse problem, comorbid anxiety, or tics Metabolized through CYP2D6
α-Adrenergic Receptor Agonists				
Clonidine extended release (Kapvay)	1 or 2	1–2	10–12	May be more effective for hyperactivity than for inattention symptoms Lessens severity of tics, especially when used in combination with methylphenidate Primary adverse effect is sedation
Guanfacine extended release (Intuniv)	1	1–2	10–12	Improves comorbid tic disorder Less sedating than clonidine Abrupt discontinuation can cause rebound hypertension

ADHD = attention-deficit/hyperactivity disorder.

Patient Case

12. The patient in question 11 has been doing well in school since methylphenidate (OROS) (Concerta) was initiated 6 months ago. His late-afternoon symptoms are well controlled; however, he has had insomnia since drug therapy initiation. Which is the best modification to his treatment regimen?

    A. Administer the Concerta dose later in the day.

    B. Change to methylphenidate modified release (Metadate CD) once a day.

    C. Change to methylphenidate transdermal patch (Daytrana).

    D. Change to atomoxetine at bedtime.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Group B *Streptococcus*, *Escherichia coli*, *Klebsiella* spp., and *Listeria* spp. are the most likely pathogens of neonatal sepsis or meningitis. Ampicillin plus ceftazidime administered at meningitic doses would provide reasonable empiric coverage (Answer B is correct). Ampicillin plus gentamicin is a reasonable alternative regimen. Cefotaxime or ceftazidime (when cefotaxime is unavailable) may be preferred to gentamicin because of its better penetration into the cerebrospinal fluid in meningitis caused by gram-negative organisms. In general, ceftazidime (or cefotaxime when available) use should be reserved for such cases because overuse of this agent has been associated with increased resistance and increased risk of invasive candidiasis. Although coagulase-negative *Staphylococcus* is the most likely cause of nosocomial neonatal sepsis, this patient's early presentation makes a hospital-acquired pathogen extremely unlikely. Therefore, vancomycin is unnecessary (Answer A is incorrect). Ampicillin plus ceftriaxone would provide adequate empiric antimicrobial coverage for the most likely pathogens. However, ceftriaxone use can result in biliary sludging, leading to reduced elimination of bilirubin and a potential risk of kernicterus in neonates (Answer C is incorrect). Ceftazidime plus gentamicin lacks coverage for *Listeria* and group B *Streptococcus,* which is still necessary empirically even though the mother received penicillin before delivery. In addition, empiric double-coverage of gram-negative organisms is not necessary for early onset neonatal sepsis (Answer D is incorrect).

2. Answer: C

Given this patient's age and culture results, the most likely infecting organism is *E. coli* or *Klebsiella* spp. (gram-negative rods), for which antimicrobial prophylaxis is not indicated (Answer C is correct). The most common pathogens causing meningitis in neonates do not warrant antimicrobial prophylaxis. If this patient were older and infected with *N. meningitidis* or *H. influenzae,* antibiotic prophylaxis with rifampin would be indicated for all close contacts, regardless of age or immunization status (Answers A and D are incorrect). Rifampin prophylaxis to eliminate nasal carriage is also indicated for people who receive index diagnoses of *N. meningitidis* and treatment with an antibiotic other than ceftriaxone (Answer B is incorrect).

3. Answer: C

The most likely causative organisms of sepsis or meningitis in this age group are *S. pneumoniae* and *N. meningitidis*. Therefore, a regimen of ceftriaxone plus vancomycin would provide appropriate empiric coverage (Answer C is correct). Depending on the regional incidence of resistant *S. pneumoniae,* empiric vancomycin might not be necessary. Ampicillin plus gentamicin would not provide adequate coverage (Answer A is incorrect). Cefuroxime does not provide reliable penetration into the cerebrospinal fluid; therefore, it would not be appropriate empiric coverage because this patient's presentation suggests that he has meningitis (Answer B is incorrect). Rifampin would be the drug of choice for the prophylaxis of close contacts if this patient receives a diagnosis of meningococcal meningitis; however, it is inadequate for treatment (Answer D is incorrect).

4. Answer: B

Palivizumab is the drug of choice for prophylaxis against RSV infection in high-risk patient populations, including those born before 29 weeks' gestation, regardless of risk factors, who are 12 months or younger during RSV season (Answer B is correct). Patients born between 29 and 32 weeks' gestation are not considered high risk because of their gestational age (Answer C is incorrect). To be considered as candidates for palivizumab prophylaxis, these infants must have a disease state (e.g., chronic lung disease, hemodynamically significant heart disease, airway anomalies, neuromuscular disease, profound immunodeficiency) that places them at risk of severe RSV infection. Other potential risk factors (e.g., siblings younger than 5 years or day care attenders) are no longer considered when determining the appropriateness of palivizumab prophylaxis. Patients with complex heart defects needing surgical repair are at high risk of developing severe RSV infections; however, after the repair is complete, palivizumab is no longer warranted (Answer D is incorrect). Patients with a history of chronic lung disease who are 24 months or younger and who are receiving, or have received in the past 6 months, oxygen or medical management for chronic lung disease are also at risk of severe RSV infection (Answer A is incorrect).

5. Answer: D

There is no specific treatment for RSV infection. Intravenous fluids, oxygen, and mechanical ventilation, if needed, are indicated (Answer D is correct). Palivizumab is the drug of choice for RSV prophylaxis, but it has no role in treatment (Answer A is incorrect). Corticosteroids have not been shown to be of benefit and are therefore not indicated (Answer B is incorrect). Secondary bacterial infection with *H. influenzae* or *M. catarrhalis* can occur; however, empiric antibiotic therapy is not indicated (Answer C is incorrect).

6. Answer: A

Persistence of middle ear fluid after an episode of AOM is common. If these findings are not associated with signs and symptoms of infection, a diagnosis of OME is made. The AAP practice guideline for the management of OME recommends watchful waiting (Answer A is correct). A watch-and-wait approach would not be appropriate for this patient if she were given a diagnosis of AOM rather than OME, because she is younger than 6 months. Spontaneous resolution of OME occurs within 3 months in 75%–90% of cases after AOM without residual morbidities. Children at high risk of speech and learning problems (e.g., craniofacial anomalies, Down syndrome, severe visual impairment) may need earlier, more aggressive intervention (e.g., tympanostomy tubes). Decongestants and antihistamines do not promote resolution or improve symptoms (Answer C is incorrect). Antibiotics are not effective in treating OME (Answer B is incorrect). However, high-dose amoxicillin (80–100 mg/kg/day) is considered first-line therapy for AOM. If this patient's treatment with the initial course of lower-dose amoxicillin fails (which is not a recommended regimen) or if she develops new signs of infection, then high-dose amoxicillin will be an appropriate treatment choice. Up to 74% of streptococcal strains have been reported to be resistant to azithromycin, which also has poor activity against *H. influenzae*; therefore, this would not be the best antibiotic option if an infection developed (Answer D is incorrect).

7. Answer: C

Four cases of otitis media in 12 months is considered recurrent otitis media, for which the watch-and-wait approach is not recommended (Answer D is incorrect). Previously, this patient would have been a candidate for antibiotic prophylaxis; however, this practice has fallen out of favor because of the significant risk of antimicrobial resistance compared with the minor reduction in the occurrence of otitis media (Answer A is incorrect). Tympanostomy tubes are typically reserved for patients in whom aggressive antibiotic therapy fails, and they may be effective only in otitis with bulging tympanic membrane (Answer B is incorrect). In addition, the greatest benefit of tympanostomy tubes is in patients with persistent OMEs resulting in significant hearing loss. As long as this patient continues to respond to high-dose amoxicillin, this will be considered a first-line regimen (Answer C is correct). In addition, the pneumococcal and influenza vaccines should be administered according to the recommended schedule, because these organisms are common causes of AOM.

8. Answer: D

Vaccines are often deferred for inappropriate reasons, leading to missed opportunities for immunization. Previous administration of IVIG can decrease the efficacy of live vaccines, such as MMR and varicella, but it does not affect the efficacy of inactivated products (Answer D is correct). The suggested interval between an IVIG dose and the administration of live vaccines depends on the immune globulin product and indication. Concerns about an association between MMR vaccine and the development of autism and immunizations overwhelming the immune system have been disproved by scientific evaluation (Answers A and C are incorrect). The MMR vaccine is grown in chick embryo tissue; however, an egg allergy is not a contraindication to its administration (Answer B is incorrect).

9. Answer: A

Immunocompromised patients should not receive live vaccines; therefore, the MMR and varicella vaccines should be deferred in these patients (Answer A is correct). Mild coldlike symptoms, or administration of antibiotics for mild illnesses, such as otitis media, are not a contraindication to vaccination, and deferring immunizations for such reasons is considered a missed opportunity (Answer B is incorrect). Patients with HIV, especially those with asymptomatic disease, should be considered candidates for all age-appropriate vaccines, including those containing live virus and the pneumococcal vaccine (Answer C is incorrect). Corticosteroid administration is an indication for deferral of live vaccines only if the patient is receiving high doses (more than 2 mg/kg/day of prednisone equivalent) for more than 14 days (Answer D is incorrect).

10. Answer: B

Rash associated with antiepileptic drugs is a common adverse effect, and it generally resolves within a few days after discontinuation. There is no reliable method to determine whether the rash will remain benign or progress to a more severe skin reaction; therefore, discontinuation of the offending drug is warranted (Answer D is incorrect). Carbamazepine has a higher incidence of rash than oxcarbazepine does, and cross-reactivity has been noted (Answer A is incorrect). Valproic acid is a good choice for managing focal seizures, and it has a low incidence of rash. However, the principal adverse effects of valproic acid include weight gain and menstrual irregularities, both of which would be undesirable in this overweight teenager. In addition, valproic acid is a known teratogen (pregnancy category D) that should be avoided if other options are available in girls of reproductive age who are unreliable in their use of contraception (Answer C is incorrect). Levetiracetam (pregnancy category C) has a low incidence of rash and minimal drug interactions (Answer B is correct).

11. Answer: A

Stimulants, especially methylphenidate, are generally considered first-line therapy for treating ADHD. Because this patient shows symptoms at school and at home, the short duration of action (3–5 hours) of a twice-daily methylphenidate immediate-release regimen will probably not provide adequate symptom relief (Answer B is incorrect). Likewise, D-methylphenidate has a short duration of action. In addition, D-methylphenidate is no more effective and has no fewer adverse effects than methylphenidate immediate release. Therefore, D-methylphenidate is generally not considered cost-effective (Answer D is incorrect). Extended-release guanfacine was recently approved by the FDA for the treatment of ADHD, but it should be reserved for patients with ADHD and tic disorders or those who have not responded to stimulant agents (Answer C is incorrect). Methylphenidate (OROS) with its longer duration of action (10–12 hours) would provide the best coverage (Answer A is correct). Therapy with this drug can be initiated without previous titration using methylphenidate immediate release.

12. Answer: C

Changing to a methylphenidate transdermal patch allows flexibility in the duration of drug effect. Wearing the patch for 9 hours results in about 12 hours of therapeutic effect; however, the patch can be removed sooner, thus reducing the duration of effect and allowing serum concentrations to decrease before bedtime (Answer C is correct). Response rates to atomoxetine are lower than to methylphenidate (OROS) in children with ADHD. In addition, the onset of therapeutic effect for atomoxetine is delayed (typically 2–4 weeks). Atomoxetine does not have the adverse effects of insomnia. Rather, fatigue and drowsiness are more common, the tolerability of which is improved with the initiation of atomoxetine at low doses with a gradual titration. The dose can also be administered in the evening to improve tolerability. Because this patient responded well to stimulant therapy with methylphenidate and there are disadvantages to atomoxetine (i.e., lower response rates and delayed onset), it would be best to manage the adverse effect of insomnia by altering the stimulant regimen (Answer D is incorrect). Administering methylphenidate OROS later in the day would probably worsen the insomnia (Answer A is incorrect). A better recommendation would be to administer methylphenidate OROS earlier in the morning, which would allow more time in the late afternoon and evening for the serum concentration to decrease before bedtime. Changing to a shorter-acting methylphenidate product (e.g., methylphenidate CD or LA) might improve the insomnia, but because of its shorter duration of action, it might compromise late-afternoon symptom control (Answer B is incorrect). In some cases, insomnia is related to rebound of ADHD symptoms when the stimulant wears off, rather than an adverse effect of the stimulant. The addition of a short-acting stimulant late in the day can help in these cases. This does not seem to apply to this patient because his late afternoon ADHD symptoms are reported to be well controlled. Counseling about proper sleep hygiene can also be an effective intervention for the management of insomnia.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B

The pathogens most likely to cause pediatric sepsis or meningitis in this age group are *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* (Answer B is correct). Group B *Streptococcus*, which often colonizes the female genitourinary tract, is a common pathogen causing neonatal sepsis (Answer C is incorrect). *Pseudomonas aeruginosa* is more commonly associated with nosocomial sepsis (Answer D is incorrect). Adolescents who develop an RSV infection typically present with mild upper respiratory tract symptoms, whereas this patient's presentation suggests meningitis (Answer A is incorrect).

2. Answer: B

Before the 2014 publication of the AAP's updated guidelines, infants who were born before 31 weeks', 6 days' gestation and who were 6 months or younger at the beginning of RSV season were considered at high risk of severe infection; therefore, routine palivizumab prophylaxis was recommended solely on the basis of their prematurity. The 2014 guidelines changed the prematurity-based criteria for routine palivizumab prophylaxis to include only infants born before 29 weeks' gestation and who are younger than 12 months at the beginning of RSV season (Answer A is incorrect). According to the new guidelines, infants born between 29 and 32 weeks' gestation must have chronic lung disease to be indicated for palivizumab prophylaxis. Additionally, infants of any gestation with hemodynamically significant congenital heart disease, airway anomalies, neuromuscular disease, or who are profound immunocompromised are considered candidates for palivizumab prophylaxis (Answer B is correct). Risk factors such as day care attendance and school-aged siblings are no longer considered when determining whether prophylaxis is warranted (Answer D is incorrect). Routine prophylaxis for otherwise healthy, full-term neonates is not recommended because evidence of benefit is lacking (Answer C is incorrect).

3. Answer: C

Prophylaxis with rifampin is recommended for close contacts of patients with *N. meningitidis* or *H. influenzae* (Answer C is correct), regardless of their immunization status (Answers B and D are incorrect). Postexposure prophylaxis against pneumococcal meningitis is not recommended (Answer A is incorrect).

4. Answer: D

All scheduled immunizations should be given during the same visit. Delaying some vaccines until a later date is considered a missed opportunity (Answer A is incorrect). Oral polio vaccine is no longer recommended as part of the routine schedule because of the risk of vaccine-associated poliomyelitis, which accounts for most newly diagnosed cases in the United States since 1979 (Answer B is incorrect). Premature neonates should be vaccinated according to chronologic age, and doses should not be reduced (Answer C is incorrect). As of 2008, influenza vaccine is recommended for all children 6 months to 18 years of age during influenza season (Answer D is correct).

5. Answer: B

Otitis media is most commonly caused by *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and viruses. Blood culture results do not predict causative organisms of otitis media (Answer A is incorrect). If the patient is older than 2 years and does not have severe symptoms (i.e., moderate to severe otalgia or body temperature of 102.2°F [39°C] or higher), delaying the decision to prescribe antibiotics is an acceptable strategy (Answer B is correct). If otalgia or fever persists for more than 48–72 hours, antibiotic therapy is acceptable, but antibiotics are not necessary if these symptoms resolve spontaneously within this time. If antibiotics are warranted and the patient does not have an allergy, high-dose amoxicillin is the treatment of choice rather than azithromycin (Answer C is incorrect). Broad-spectrum antibiotics such as ceftriaxone should be reserved for resistant cases (Answer D is incorrect).

6. Answer: D

In general, patients who do not respond to one stimulant agent should be treated with a different stimulant before they are considered not to have responded to this class of drug therapy. However, switching from a methylphenidate-containing stimulant to extended-release mixed amphetamine salts (a different stimulant) should be avoided in this patient, because amphetamine-containing products have been associated with SCD

in children with structural heart defects (Answer B is incorrect). The methylphenidate transdermal system has a duration of action and efficacy similar to those of methylphenidate OROS; therefore, it is unlikely to benefit this patient because her therapy with methylphenidate immediate release and methylphenidate OROS has already failed (Answer C is incorrect). If adherence or difficulty swallowing pills were a suspected cause of treatment failure in this patient, a patch might be a reasonable alternative. Clonidine can be added as an adjunctive therapy for patients whose treatment with a single stimulant agent fails; however, it should not be used as the sole agent for treating ADHD (Answer A is incorrect). Atomoxetine, which is not a stimulant, would be a reasonable alternative to the stimulant class of agents in this patient, because some patients respond better to one class of agent than another (Answer D is correct).

7. Answer: A

Valproic acid is considered a first-line therapy for treating absence seizures. If the patient is having breakthrough seizures on ethosuximide—also a first-line therapy—and the dose has been maximized, it is reasonable to switch to valproic acid (Answer A is correct). Phenytoin, phenobarbital, and gabapentin have not been shown effective in treating absence seizures (Answer B, C, and D are incorrect).

8. Answer: C

	Adverse Event (loss of appetite)	
	Yes	No
Exposure (stimulant)		
Yes	7 (*a*)	193 (*b*)
No	1 (*c*)	197 (*d*)

Odds ratio = (*a*/*c*)/(*b*/*d*)
= (7/1)/(193/197)
= 7.15

9. Answer: C

A case series does not reliably establish a causal relationship, but it suggests a potential hypothesis to be studied further (Answer A is incorrect). Given the current knowledge about the potential risk of kernicterus related to ceftriaxone use, obtaining investigational review board approval for a randomized controlled or a crossover trial design would be difficult, given ethical considerations, although this study design is the gold standard for establishing a causal relationship (Answers B and D are incorrect). Therefore, a retrospective cohort would be best to investigate a causal relationship in this instance (Answer C is correct).

10. Answer: D

Patients with congenital heart defects, particularly those with hemodynamically significant lesions, are at high risk of severe RSV infection regardless of their gestational age (Answer A is incorrect). These patients are considered to be at high risk if they are younger than 12 months at the beginning of RSV season and have not undergone definitive surgical repair of their heart defect. Although this patient had surgery for his congenital heart defect, he will require another operation for complete repair (Answer C is incorrect). It is not recommended that palivizumab be initiated as routine prophylaxis in hospitalized patients because it does not reduce the incidence of nosocomial-acquired RSV infection (Answer B is incorrect). However, patients currently receiving a course of palivizumab (one dose per month for 5 months) at the time of hospital admission should have that intervention continued. In addition, cardiopulmonary bypass reduces palivizumab serum concentrations; therefore, patients undergoing congenital heart defect repair during RSV season should receive a postoperative dose of palivizumab as soon as they are medically stable, regardless of when their next scheduled dose is due (Answer D is correct).

Policy, Practice, and Regulatory Issues

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Learning Objectives

1. Identify the congressional committees, government agencies, and regulatory and oversight bodies that govern health care in the United States.
2. Explain recent federal legislative and regulatory activity that affects the delivery of health care.
3. Describe the regulatory actions that govern the prescription drug approval process and the conduct of human subjects research.
4. Describe national quality initiatives aimed at improving health care delivery and patient health outcomes.
5. Explain medication policy implications at an institutional level.

Abbreviations in This Chapter

ACA	Patient Protection and Affordable Care Act of 2010
AHRQ	Agency for Healthcare Research and Quality
ANDA	Abbreviated new drug application
BPCIA	Biologics Price Competition and Innovation Act
CDER	Center for Drug Evaluation and Research
CER	Clinical effectiveness research
CFR	Code of Federal Regulations
CHIP	Children's Health Insurance Program
CMS	Centers for Medicare and Medicaid Services
CoP	Conditions of Participation
DHHS	Department of Health and Human Services
DQSA	Drug Quality and Security Act of 2013
ETASU	Elements to Assure Safe Use
FD&C Act	Food, Drug, and Cosmetic Act of 1938
HEDIS	Healthcare Effectiveness Data and Information Set
HIPAA	Health Insurance Portability and Accountability Act of 1996
HITECH	Health Information Technology for Economic and Clinical Health Act
INDA	Investigational new drug application
IRB	Institutional review board
MACRA	Medicare Access and CHIP Reauthorization Act of 2015
MUE	Medication use evaluation
NDA	New drug application
NQF	The National Quality Forum
PHI	Protected health information
PSO	Patient safety organization
REMS	Risk Evaluation and Mitigation Strategies

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. Which congressional committee is responsible for deciding how much funding the National Institutes of Health (NIH) receives as part of the 21st Century Cures Act?
   A. House and Senate Appropriations
   B. House Energy & Commerce
   C. Senate Health, Education, Labor, and Pensions (HELP)
   D. House Ways & Means

2. Which of the following health care practices is not regulated by the Department of Health and Human Services (DHHS) or one of its agencies?
   A. Research involving human subjects
   B. Health Insurance Portability and Accountability Act of 1996 (HIPAA) provisions to protect identifiable health information
   C. The diversion of controlled substances
   D. Inspection of drug manufacturers for compliance and good manufacturing processes

3. The Drug Quality and Security Act (DQSA) of 2013 differentiated a traditional compounder from an outsourcing facility. Which of the following characteristics is unique to traditional compounders?
   A. Subject to U.S. Food and Drug Administration (FDA) registration and inspection
   B. Required to follow good manufacturing practices for compounding
   C. Compounded for identified individual patient
   D. Exempt from track-and-trace requirements

4. Which is the best description of the Safe and Secure Drug Disposal Act of 2010?
   A. Authorizes hospitals and clinics with on-site pharmacies and retail pharmacies to become collectors

B. Authorizes DHHS to promulgate rules for patient disposal of unused controlled substances

C. Requires all collectors to register as reverse distributors

D. Requires current Drug Enforcement Administration (DEA) registrants to become collectors

5. The Medicare Access and CHIP Reauthorization Act (MACRA) of 2015 includes which of the following provisions?

A. Establishment of alternative payment models and a merit-based incentive payment system

B. Provision of a financial incentive to eligible professionals and eligible hospitals to begin the "meaningful use" of electronic health records

C. Creation of an optional Medicaid State Plan benefit, allowing states to establish Health Homes for Medicaid patients with chronic conditions

D. Creation of the Centers for Medicare and Medicaid Services (CMS) Innovation Center to pioneer novel care delivery and payment models

6. Which option correctly describes when an Investigational New Drug Application (INDA) should be submitted to the FDA?

A. Before preclinical studies

B. After preclinical studies but before phase I clinical trials

C. During phase II studies

D. After phase III studies but before market approval

7. Which of the following statements regarding generic drugs and their approval process is true?

A. New Drug Applications (NDAs) for generic drugs are submitted to the FDA's Center for Drug Evaluation and Research after 3–5 years of market exclusivity.

B. Drug manufacturers are required to demonstrate therapeutic equivalence in an Abbreviated New Drug Application (ANDA) for a generic drug.

C. Once approved, the generic and brand manufacturers retain a 90-day exclusivity period.

D. An authorized generic is produced by the brand company under the NDA but marketed as a generic.

8. Regarding the evaluation of medications for interchange in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book), which statement is most accurate?

A. Products with an A rating are pharmaceutical equivalents only and may not be interchanged.

B. Interchangeable products may vary in dosage form and route of administration.

C. Products with a B rating are pharmaceutical equivalents and bioequivalents and may be interchanged.

D. Interchangeable products may vary in their release mechanism or excipients.

9. With respect to reporting for adverse drug experiences, which is the best option to correctly describe the purpose of MedWatch Form FDA 3500A?

A. It is for voluntary reporting by health care professionals of a serious adverse event, product quality problem, or product use error with an FDA-regulated drug, biologic, medical device, or dietary supplement.

B. It is for consumer reporting of adverse drug experiences.

C. It may contain patient identifiers and still comply with the HIPAA Privacy Rule.

D. It is the form that must be submitted by investigational new drug (IND) reporters, manufacturers, distributors, importers, and facility personnel.

10. A patient with nonvalvular atrial fibrillation is prescribed rivaroxaban for stroke prevention. The patient is later initiated on rifampin, which increases rivaroxaban hepatic metabolism through cytochrome P450 3A4 and induction of P-glycoprotein, causing a subtherapeutic serum concentration of rivaroxaban, which in turn causes the patient to develop a stroke. Which best describes this interaction?

A. Side effect

B. Adverse drug reaction (ADR)

C. Preventable adverse drug event (ADE)

D. ADE

11. Which option best describes the development and maintenance of quality measures?

A. The Joint Commission is responsible for developing and maintaining the Healthcare Effectiveness Data and Information Set (HEDIS).

B. The Patient-Centered Outcomes Research Institute (PCORI) developed the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey.

C. The National Quality Forum (NQF) is responsible for assessing and endorsing quality standards.

D. The National Committee for Quality Assurance (NCQA) is responsible for developing and maintaining the National Hospital Quality Measures.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination: Content Outline.

1. Domain 1: Patient-Centered Pharmacotherapy
    a. Task 1: Develop patient-centered, evidence-based pharmacotherapy plans. Knowledge of d
2. Domain 3: Healthcare Systems and Population Health
    a. Task 1: Implement effective medication use systems in order to improve system- and population-based pharmacotherapy: Knowledge of a, b, e
    b. Task 3: Incorporate public health initiatives to improve population health: Knowledge of b, c
    c. Task 4: Support implementation of pharmacotherapy-related quality improvement projects to foster the safe, effective, and economical use of medications. Knowledge of a, c, d

OVERVIEW

The purpose of this review of policy, practice, and regulatory issues is to highlight areas of importance for clinical pharmacists as they pertain to policies governing patient care delivery and clinical research activity. Specifically, this chapter addresses rules, regulations, and quality initiatives at the institutional and national levels.

I. CONGRESSIONAL OVERVIEW, COMMITTEES WITH JURISDICTION OVER HEALTH-RELATED POLICY, AND THE LEGISLATIVE PROCESS

A. The U.S. Congress is bicameral, with two legislative chambers: the Senate and the House of Representatives.

B. The Senate is composed of 100 elected voting members. Legislation and tasks are divided into 20 standing committees, 68 subcommittees, and 4 joint committees. The committees that have jurisdiction over health-related policy include:
   1. The Appropriations Committee, which writes the legislation that allocates federal funds to the many government agencies, departments, and organizations on an annual basis and, in particular, funds discretionary programs
   2. The Finance Committee, which has jurisdiction over issues that pertain to taxation and health programs under the Social Security Act, including Medicare, Medicaid, and the Children's Health Insurance Program (CHIP)
   3. The HELP Committee, as it pertains to health, authorizes agencies, institutes, and programs under the DHHS, which includes the FDA, NIH, and Centers for Disease Control and Prevention (CDC)
   4. The Committee on Veterans' Affairs, which oversees veteran's issues, including the Veterans' Affairs health system.
   5. The Aging Committee, which was initially established as a temporary committee but transitioned to a permanent special committee without legislative authority for matters relating to older Americans.
   6. Legislation is reviewed by the committee with the greatest jurisdiction over the provisions in the bill. For example, the Pharmacy and Medically Underserved Areas Enhancement Act (S. 314), introduced in the Senate in 2015, was referred to the Committee on Finance because it amends the Medicare program.

C. The House of Representatives is composed of 435 elected voting members and 6 delegates from the U.S. territories and from Washington, D.C., with nonvoting privileges. Legislation and tasks are divided into 20 standing committees, 4 joint committees, and 1 select committee. Several committees have jurisdiction over health-related policy:
   1. Appropriations has jurisdiction similar to that listed above.
   2. Ways and Means has jurisdiction over taxation and most programs authorized by the Social Security Act, similar to the Senate Finance Committee.
   3. Energy and Commerce, the oldest standing committee of the House of Representatives, has oversight of DHHS and is similar to the Senate HELP Committee.
   4. Veterans' Affairs oversees issues related to veterans' concerns.
   5. Legislation is sent to any committee that has jurisdiction over any of the provisions in the bill. For example, the companion bill to S. 109, the Pharmacy and Medically Underserved Areas Enhancement Act (H.R. 592), introduced in the House in 2015, was referred to the Subcommittees on Health in both the Energy and Commerce and Ways and Means committees.

D. Legislative Process (Figure 1)
   1. Legislation is drafted by a member of Congress, a congressional committee, a constituent, a state legislature, or an executive communication from the president or an administrative agency.

2. Types of legislation:
    a. Bills are introduced into either the House or the Senate (prefixed H.R. or S., respectively) as one of two types:
        i. Authorization bills grant authority for a program or agency to exist or to promulgate regulations. Once approved, authorization bills will ultimately need an appropriations bill to be introduced and approved in order to receive funding.
        ii. Appropriation bills designate and commit a sum of money designated for a particular purpose by an act or bill.
        iii. Either of these types of bills may be introduced as companion bills, such as the Pharmacy and Medically Underserved Areas Enhancement Act, may be introduced separately or simultaneously into the House and Senate.
    b. Once introduced, the legislation is generally referred to the relevant committees for consideration, markup, and approval.
    c. Action, debate, and voting on legislation, which are dictated by rules, differ greatly between the Senate and the House of Representatives.
    d. Because identical versions of a bill must be approved by the two chambers, conference committees work to draft a compromise bill, acceptable to both chambers, that will go to the president.

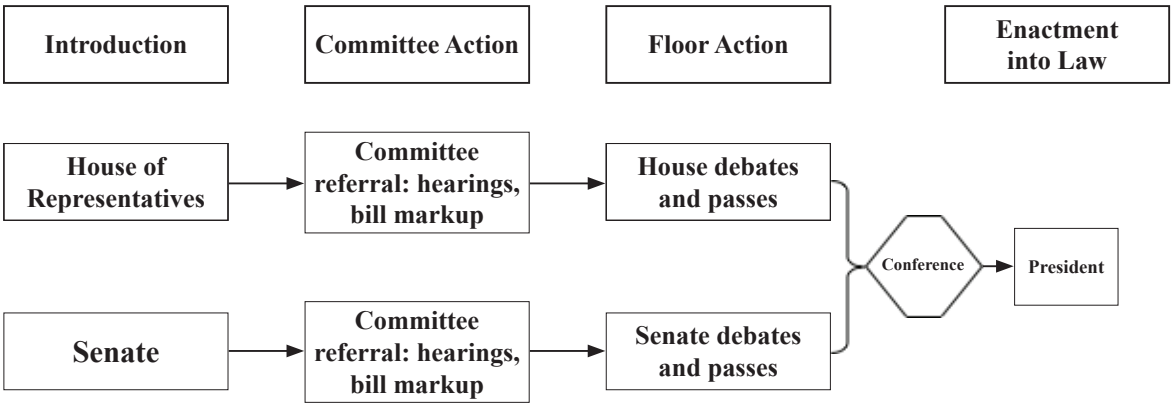

Figure 1. Legislative process.

E. Creation and codification of regulation by the authorized U.S. government department or agency is discussed in the next section.

F. Types of appropriations, or funding:
    1. Mandatory spending, representing government spending on certain programs that are required by law, includes:
        a. Entitlement spending, which authorizes funding to be appropriated for the amount needed to meet the need of those entitled to the benefit for programs such as Medicare, Medicaid, and Social Security; exact levels are automatically set on the basis of the number of eligible recipients, with amounts changed only with eligibility criteria changes
        b. Direct spending, which includes funding required specifically by an authorization bill
    2. Discretionary spending levels are determined annually by Congress; spending is optional. DHHS agencies such as the FDA are funded through discretionary spending.
    3. Continuing resolution maintains funding for a program if the congressional fiscal year, ending September 30, ends without a new appropriation in place.

II. U.S. GOVERNMENT DEPARTMENTS AND AGENCIES WITH PRIMARY REGULATORY IMPACT ON THE PRACTICE OF PHARMACY

A. The executive branch comprises the president's cabinet and the heads of 15 executive departments, including DHHS, the Department of Justice (DOJ)—which includes the Office of the Attorney General—and the Department of Veterans' Affairs.

B. The Department of Health and Human Services (DHHS) is the agency charged with protecting the health of Americans. The following agencies are part of DHHS:
   1. The FDA is responsible for the safety of most foods (human and animal) and cosmetics, and it regulates both the safety and the effectiveness of human drugs, biologics (e.g., vaccines, blood products, therapeutic proteins), medical devices, and animal drugs.
   2. The Centers for Medicare and Medicaid Services (CMS) administers Medicare, Medicaid, and CHIP. It drives the Value-Based Purchasing (VBP) Program, the Medicare Shared Savings Program (MSSP), and the Electronic Health Record (EHR) Meaningful Use Incentive Program, and it develops Conditions of Participation (CoP) and Conditions for Coverage that health care organizations are required to meet in order to participate in Medicare and Medicaid programs. However, Medicare is considered an "entitlement" program, and appropriations made to CMS are not "discretionary" from a budgetary standpoint.
   3. The Agency for Healthcare Research and Quality (AHRQ) supports research that helps people make better-informed decisions and improves the quality of health care services. The Public Health Service Act of 1998 authorized AHRQ to convene the U.S. Preventive Services Task Force (USPSTF). The USPSTF is an independent panel of experts on evidenced-based practices for preventive health care who develop clinical recommendations for preventive services.
   4. The CDC provides programs that reduce the health and economic consequences of the leading causes of death and disability. An example is Healthy People, which provides science-based national goals and objectives with 10-year targets designed to guide national health promotion and disease prevention efforts.
   5. The Health Resources and Services Administration (HRSA) improves access to health care through programs that strengthen the health care workforce, build healthy communities, and achieve health equity for people who are geographically isolated and/or economically or medically vulnerable. HRSA houses the National Center for Health Workforce Analysis, charged with estimating the supply and demand for health care workers and designating shortage criteria in order to establish Health Professional Shortage Areas or Medically Underserved Areas or Populations.

C. The DOJ has jurisdiction over the DEA, which prevents, detects, and investigates the diversion of controlled substances and monitored chemicals.

D. The U.S. Environmental Protection Agency (EPA) seeks to protect human health and the environment.
   1. Through the Resource Conservation and Recovery Act of 1976, the EPA has jurisdiction over rules governing the disposal of solid and hazardous waste.
   2. The Management Standards for Hazardous Waste Pharmaceuticals Rule proposes new regulations for health care facilities (including pharmacies) and reverse distributors in the handling of hazardous waste pharmaceuticals in order to improve environmental protection.

E. Departments and agencies of the U.S. government make rules and adjudicate them within areas of delegated authority.
   1. The Administrative Procedure Act of 1946 granted agencies of DHHS the power to promulgate rules and regulations that have the effect of substantive law.
   2. Proposed codification of general and permanent rules is published in the Federal Register, and the public is allowed to provide feedback during a prespecified period.

3. Final rules are published in the CFR, which has 50 titles that are updated every year on a staggered basis.
    a. Title 21: Food and Drugs
        i. Contains rules related to the FDA, DEA, DOJ, and Office of National Drug Control Policy
        ii. Pregnancy and Lactation Labeling Rule (21 FDA CFR Part 201) requires changes to the content and format for drug labeling to assist in the risk-benefit assessment for medication use related to pregnancy and lactation and includes the removal of pregnancy letter categories.
        iii. Institutional Review Boards (21 FDA CFR Part 56) contain standards for the composition, operation, and responsibility of an IRB that reviews and approves of studies for products regulated by the FDA and regulates human subjects research that involves an investigational drug or device or when an approved product is being used in an investigation. This rule includes clinical investigations designed for submission to the FDA in support of an application or marketing permit. Differences exist between this regulation and that of the Common Rule (Title 45) for the definitions of research, human subjects, and IRB (discussed later). Both must be considered in the conduct of research.
        iv. Disposal of Controlled Substances (21 CFR DOJ DEA Parts 1300, 1301, 1304, et al.) governs the secure disposal of controlled substances by DEA registrants and ultimate users.
    b. Title 42: Public Health
        i. Contains rules related to DHHS, CMS, and the HHS Office of Inspector General (OIG) (which fights fraud, waste, and abuse among DHHS programs)
        ii. Federally qualified health centers and organizations that receive grants for enhanced reimbursement from Medicare and Medicaid for offering health care services to all patients, regardless of their ability to pay, are regulated by rules outlined in Medicare CMS regulations in Title 42.
        iii. Changes in Provider and Supplier Enrollment, Ordering and Referring, and Documentation Requirements; and Changes in Provider Agreements for CMS (42 CFR DHHS CMS parts 424 and 31) expand the definition of non-physician practitioners on hospital staffs to include pharmacists.
    c. Title 45: Public Welfare
        i. Common Rule (45 CFR Part 46): Federal Policy for the Protection of Human Subjects (recently updated in January 2017) protects human subjects involved in research conducted or sponsored by any agency within the DHHS (discussed later). It defines an IRB in the context of the rule and is different from that of 21 CFR 56.
        ii. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) (45 CFR Parts 160, 162, and 164) protects PHI.
            (a) It is enforced by the DHHS Office for Civil Rights.
            (b) The suite of HIPAA regulations for patient privacy and security is outlined in the Transactions and Code Set Standards, Identifier Standards, Privacy Rule, Security Rule, Enforcement Rule, and Breach Notification Rule.
4. The FDA Guidance Documents
    a. After issuing a regulation, the FDA may determine that stakeholders, including industry and academia, need more information or "guidance" on how the agency plans to uphold the regulation. As such, guidance documents represent the FDA's current perspective on a topic and interpretation of an FDA policy.
    b. The FDA guidance documents are not laws. As such, they do not amend the CFR or undergo the same notice and comment process as regulations themselves.
    c. Similarly, the documents are not binding if alternative approaches satisfy regulations.

III. RECENT LEGISLATIVE ACTIVITY WITH REGULATORY AND HEALTH POLICY IMPLICATIONS

A. The American Recovery and Reinvestment Act (ARRA) of 2009 includes the Health Information Technology for Economic and Clinical Health (HITECH) Act.
   1. The HITECH ACT authorizes DHHS to create programs to improve health care quality, safety, and efficiency through the promotion of health information technology, including EHRs and health information exchanges (HIEs) to facilitate and expand the secure electronic movement and use of health information among organizations in accordance with nationally recognized standards.
      a. An HIE is defined as a process for exchanging health information through one of three ways:
         i. Directed exchange: Ability to send and receive secure information electronically between care providers to support coordinated care (e.g., allows a primary care provider to send a medical summary to a specialist during a referral)
         ii. Query-based exchange: Ability of providers to find and/or request information on a patient from other providers (e.g., allows emergency department providers to retrieve individual patient records after patient consent)
         iii. Consumer-mediated exchange: Ability of patients to aggregate and control the use of their health information among providers (e.g., online portals that allow patients to track results and update demographic or health information)
      b. A health information organization (HIO) is a model for exchanging information at the local, regional (known as a RHIO [regional health information organization]), or state level.
      c. The HITECH Act created the Office of the National Coordinator for Health Information Technology to coordinate nationwide standards and implementation efforts to increase the interoperability, functionality, utility, and security of health information technology and to support its meaningful use.
   2. Under ARRA, CMS issued the Electronic Health Records Incentive Programs to provide a financial incentive to health care professionals, hospitals, and Medicare Advantage Organizations that are "meaningful users" of EHRs.
      a. Meaningful users meet several objectives that demonstrate both the use of certified EHRs in a meaningful manner (e.g., e-prescribing) and those that demonstrate the use of certified EHR technology for electronic exchange of health information.
         i. Opportunities for pharmacists include the provision of medication reconciliation for patients at transitions of care.
         ii. Meaningful use requires provider-generated prescriptions to be queried against a drug formulary and submitted to pharmacies electronically.
      b. Meaningful use was absorbed into the merit-based incentive program (MIPS) created by MACRA that further modifies reimbursement. It has also since been re-named "promoting interoperability". The program now emphasizes e-prescribing, health information exchanges, provider-to-provider interoperability of records, as well as public health and clinical data exchange.
   3. The HITECH Act also imposes penalties for breaches of HIPAA and PHI, enforced by the Office for Civil Rights within DHHS.

B. The Patient Protection and Affordable Care Act of 2010 (ACA) contains several provisions, ranging from protecting consumers to improving health care quality and lowering costs to increasing access to care.
   1. It mandates that new health plans cover USPSTF recommendations receiving a high rating of grade of A or B at no cost to patients
   2. The Medicare Shared Savings Program offers providers and systems the opportunity to participate in accountable care organizations (ACOs). ACOs are a set of providers associated with a defined population of patients accountable for the quality and cost of care delivered to that population. Pharmacists may aid ACOs in achieving these quality goals.

3. The ACA provides opportunities for pharmacists to participate in the Medicare Annual Wellness Visit.
4. The ACA created the CMS Innovation Center to pioneer novel care delivery and payment models in which opportunities for pharmacists may exist:
    a. The Comprehensive Primary Care Plus (CPC+) initiative explores whether reimbursable comprehensive primary care can result in better outcomes at reduced costs. Current CPC+ guidelines require that participating practices develop a plan to provide comprehensive medication management to patients discharged from the hospital and those receiving longitudinal care management. The CPC+ initiative laid the foundation for the Primary Care First initiative – a voluntary 5-year payment model launched in early 2020 with the first performance period beginning in January 2021.
    b. The Independence at Home Demonstration Program promotes the interdisciplinary collaboration of clinicians to provide home-based medical care for Medicare beneficiaries and tests the effectiveness of delivering comprehensive primary care services at home to determine whether doing so improves care for Medicare beneficiaries with multiple chronic conditions.
    c. Future CMS value-based initiatives will likely focus on hospitals assuming a greater level of risk.
5. The ACA also created an optional Medicaid State Plan benefit that allows states to establish Health Homes to provide comprehensive care for Medicaid patients with chronic conditions.

C. The Physician Payments Sunshine Act (i.e., Sunshine Act) authorized CMS to require manufacturers of drugs, medical devices, and biologicals that participate in federal health care programs to report payments and items of value given to physicians and teaching hospitals. It also requires manufacturers and group purchasing organizations to report physician ownership or investments as part of the Open Payments Program.

D. The Safe and Secure Drug Disposal Act of 2010
    1. This legislation authorized the DEA to promulgate rules for patient and long-term care facility disposal of unused controlled substances.
    2. The Disposal of Controlled Substances Final Rule allows the transfer of unwanted and unused controlled substances from an ultimate user (i.e., patient) to an authorized collector for safe, secure, and responsible disposal. Authorized collectors include manufacturers, distributors, reverse distributors, narcotic treatment programs, hospitals and clinics with on-site pharmacies, and retail pharmacies, including long-term care facilities and specialty pharmacies.
        a. Allows ultimate users to voluntarily dispose of controlled substances through take-back and mail-back events and in collection receptacles
        b. Regulates each element of the disposal process, including transfer, delivery, collection, return, and recall of controlled substances

E. The FDA Safety and Innovation Act of 2012
    1. Addresses the drug approval pathway by:
        a. Authorizing the Generic Drug User Fee Act and the Biosimilar User Fee Act to collect fees for product applications, supplements, and other services in addition to reauthorizing the Prescription Drug User Fee Act of 1992 (PDUFA) through 2017
        b. Establishing the "breakthrough therapy" drug approval pathway
        c. Increasing stakeholder involvement in FDA processes by providing for the establishment of a patient-focused drug development initiative
        d. Permanently incentivizes pediatric drug studies to enhance accurate labeling
    2. Addresses drug shortages by:
        a. Requiring a drug manufacturer to report permanent discontinuation (that may disrupt U.S. supply) of drug manufacture that is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, at least 6 months prior

b. Includes provisions for failure to report a shortage, expediting manufacturer inspections, publishing a drug shortage list, authorizing hospitals to repackage drugs without registering as an establishment if distributing within a health system, and requiring study of the impact of medication shortages

F. The Drug Quality and Security Act (DQSA) of 2013
   1. Establishes a new section (503B) in the Food, Drug, and Cosmetic Act of 1938 (FD&C Act) to allow a compounding facility to voluntarily register as an outsourcing facility with the FDA (Table 1).
      a. The outsourcing facility must give a licensed pharmacist direct oversight over compounded drugs.
      b. Among other requirements, only drugs with bulk ingredients listed as approved by the secretary may be compounded; also, the facility must report to the secretary every six months and undergo inspection by the FDA, report serious adverse events, and label products identifying them as compounded drugs.
   2. Adds a new section (582) to the FD&C Act with product-tracing requirements ("track and trace").
      a. These requirements apply to drug manufacturers, repackagers, wholesale distributors, and dispensers to provide transaction details when pharmaceutical products change ownership.
      b. Entities must also respond promptly in the event of a recall or suspicion or investigation of an illegitimate product.
      c. This legislation demonstrates the utility of FDA guidance documents. For example, in August 2017 the FDA released a draft guidance document highlighting that a pharmacy found to be selling medication to another pharmacy in the absence of a patient-specific need would be serving as both a dispenser and a wholesale distributor. This example highlights the utility of both the guidance documents themselves as well as the comment process to pharmacists.

Table 1. Basic Comparison of Compounding of Drug Products Under Sections 503A and 503B

Category	503A: Traditional Compounder	503B: Outsourcing Facility
FDC Act exemptions	Good manufacturing practices Specific labeling requirements FDA approval before marketing	Specific labeling requirements FDA approval before marketing
Compounding practice	Compounded for identified individual patient Must follow USP guidance for compounding	Sterile compounding May or may not obtain prescriptions for individual patients Must follow good manufacturing practices for compounding
Reporting and registration	No reporting or registration Must follow track-and-trace requirements	FDA registration voluntary Reports of compounded products and bulk ingredients every 6 months Exemption from track-and-trace requirements
Fees	None	Establishment and inspection fees
Shipping restrictions	Under state regulations	None

FDA = U.S. Food and Drug Administration; USP = United States Pharmacopeia

G. Medicare Access and CHIP Reauthorization Act (MACRA) of 2015
   1. Repealed the sustainable growth rate (SGR) physician reimbursement methodology, where excess spending in one year could lower reimbursements in the following year, which threatened to reduce Medicare physician payments for more than a decade

2. Represents a shift in reimbursement from fee-for-service to pay-for-performance or pay-for-value:
    a. Establishes an alternative payment model (APM) for physicians participating in patient-centered medical homes (PCMHs), ACOs, and Medicare shared-savings programs
    b. Establishes MIPS, which reimburses on the basis of quality, resource use, clinical practice improvement activities, and meaningful use of EHR
        i. Sunsets three existing value-based payment adjustments: the EHR incentive program ("meaningful use," now called "promoting interoperability"), the Physician Quality Reporting System, and Value-Based Payment Modifier (discussed later) and combines them into MIPS
        ii. Bases payment rate on provider performance in four categories—quality, advancing care information (includes "promoting interoperability"), improvement activities (emphasizes PCMH participation), and cost
    c. The Medicare Access and CHIP Reauthorization Act (MACRA) of 2015 also reauthorized CHIP through fiscal year 2017.

H. 21st Century Cures Act
1. The act is aimed at streamlining approvals through several initiatives, including a limited population pathway for anti-infectives, accelerated approval for regenerative therapy, the use of new designs in FDA approvals (e.g., common control arm for multiple trials to speed recruitment and new statistical models to shorten approval time), encouragement of the FDA to review and share pathways for biomarkers and outcome assessment methods that may expedite review, and streamlining of differences between the DHHS and FDA human subjects' protection rules and IRBs, approval of combination products, and approval of high-risk medical devices.
2. The Cures Act is also aimed at including the patient voice/experience into approval data and processes while allowing the compassionate use of investigative drugs for outside clinical trials in terminally ill patients.
3. The act encourages innovation through the sharing of data by NIH funding recipients and reduces burden on researchers by excluding NIH researchers from the Paperwork Reduction Act.
4. The act addresses workforce provisions, including ensuring that women, children, and racial/ethnic minorities are appropriately represented in clinical research and by supporting the NIH's Next Generation Researchers Initiative.
5. The act supports high-priority NIH initiatives such as the Brain Research through Advancing Innovative Neurotechnologies (BRAIN), Precision Medicine, and Cancer Moonshot initiatives and recommends new initiatives such as antimicrobial resistance monitoring by the CDC.
6. The act increases funding for mental health, opioid addiction treatment, and the NIH. This funding is discretionary and requires annual Congressional approval.

I. The Comprehensive Addiction and Recovery Act (CARA) of 2016
1. Comprehensive effort to address the opioid epidemic, encompassing prevention, treatment, recovery, law enforcement, criminal justice reform, and expansion of naloxone availability for overdose reversal
    a. Important for pharmacists, this bill creates funding mechanisms to encourage pharmacies to strategize and dispense opioid overdose reversal drugs pursuant to a standing order as well as to develop and provide training on administration and availability.
    b. The bill also notably expands the availability of naloxone to law enforcement agencies and other first responders, expands disposal sites for unwanted prescription medications, and established DHHS's Task Force on Pain Management.
    c. Funding to support its implementation must be appropriated annually.

J. The FDA Reauthorization Act of 2017 (S. 934, H.R. 2430): This act amends the FD&C Act to revise and extend the user fees for prescription drugs, medical devices, and biosimilar/biologic products through 2022.

K. Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017
   1. Under this act, patients with a life-threatening condition who have exhausted FDA-approved treatment options and who are unable to participate in a clinical trial for the drug may be eligible to receive the medication outside of clinical trials, provided that the drug has cleared Phase I trials and is under FDA review or is under clinical investigation intended to support FDA approval.
   2. The act amended the FDA's current individual patient expanded access process, which required that a treatment plan be submitted to the FDA for review and revision, approval from the manufacturer be secured, informed consent be obtained, and oversight be provided by an Institutional Review Board (IRB).
   3. To date, few patients have actually benefited from the Right to Try Act because most requests for investigational treatments are still being processed through the FDA expanded access pathway.

L. Helping Ensure Access for Little Ones, Toddlers and Hopeful Youth by Keeping Insurance Delivery Stable Act (Healthy Kids Act) of 2018: Reauthorizes CHIP through 2023.

M. Patient Right to Know Drug Prices and Know the Lowest Price Acts of 2018
   1. Prohibits use of "gag clauses" by insurers and pharmacy benefit managers, which prevented pharmacies from providing drug price information to patients
   2. Allows pharmacy to inform patient when cash price is lower than insurance copay

N. Coronavirus Aid, Relief, and Economic Security Act (CARES Act)
   1. Legislation to address COVID-19 pandemic, which included provisions for drug shortages
   2. Incorporated many components from two previously introduced bills, "Mitigating Emergency Drug Shortages Act (S. 2723)" and "Preventing Drug Shortages Act (H.R. 6080)," which were still being considered at the time of the CARES Act passage
   3. Enacted the following requirements:
      a. Priority FDA reviews for generic drugs in shortage
      b. Annual reporting by the FDA to Congress actions that could encourage increased manufacturing of shortage drugs, including domestic manufacturing of finished dosage forms and active pharmaceutical ingredients
      c. Mandatory manufacturer reporting of shortages, including precipitating events, anticipated extent and duration, and expected impact
      d. Manufacturer risk and redundancy plans for supply chains

IV. THE U.S. FOOD AND DRUG ADMINISTRATION AND THE PRESCRIPTION DRUG APPROVAL PROCESS

A. The Basics of the FDA and the Prescription Drug Approval Process
   1. Most federal laws that authorize the FDA to promulgate rules are enacted by amendments to the FD&C Act, and they are organized in Title 21 of the CFR.
   2. The FDA is funded through discretionary spending every fall in the appropriations bill written by the Senate and House appropriations committees, but the Senate HELP and the House Energy and Commerce committees have jurisdiction over its reauthorization.
   3. Organized by the Office of the Commissioner, Medical Products and Tobacco, Foods and Veterinary Medicine, and Global Regulatory Operations and Policy. The following offices and centers affect medication use:

a. The Office of the Commissioner conducts overall agency coordination; the FDA's top official, the commissioner, requires Senate confirmation.
b. The Office of Regulatory Affairs, the largest office, regulates all inspection and enforcement activities.
c. The National Center for Toxicological Research supports the six product centers with scientific technology, training, and technical expertise.
d. The Center for Drug Evaluation and Research (CDER) regulates prescription and nonprescription drugs.
e. The Center for Biologics Evaluation and Research (CBER) regulates biologic products, including vaccines, blood products, and gene therapy.
f. The Center for Devices and Radiological Health regulates medical devices.
g. The Center for Food Safety and Applied Nutrition regulates most foods, food additives, infant formulas, dietary supplements, and cosmetics.
h. The Center for Tobacco Products regulates tobacco-containing products.
i. The Center for Veterinary Medicine regulates feed, drugs, and devices used for pets, farm animals, and other animals.

4. Definitions
   a. A clinical trial is a research study of humans conducted to answer specific questions about vaccines, new therapies, or new ways of using known treatments. Clinical trials are required by the FDA to determine whether new drugs or treatments are both safe and effective.
   b. An INDA is submitted to the FDA's CDER for a new drug, a new indication, or an off-label use that will be used in a clinical investigation's preclinical development for that drug to be distributed across state lines for its preclinical development.
   c. A NDA is submitted to the FDA's CDER and is the vehicle by which drug sponsors formally propose that the FDA conduct a full review to approve a new pharmaceutical for sale and marketing in the United States.
   d. The ANDA contains data that, when submitted to the FDA's CDER, Office of Generic Drugs, permit the review and ultimate approval of a generic drug product.
   e. An authorized generic drug is a listed drug that is marketed, sold, or distributed directly or indirectly to the retail class of trade. Its labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, and/or trademark differs from that of the listed drug.
   f. A biologics license application is submitted to the FDA's CBER and contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology, and medical effects of a biologic product (monoclonal antibodies, enzymes, immunomodulators, growth factors, and cytokines) for which approval to market in the United States is being sought.
   g. The interchangeability of a biosimilar product may allow it to be substituted for the legend (brand) biologic with an expectation that the same clinical outcome will occur and without the requirement of notification or intervention of a prescriber.

B. History of the Regulation of Drugs and Human Subjects Research
   1. The Drug Importation Act of 1848: Prohibited the importation of unsafe or adulterated drugs at key ports of entry
   2. The Pure Food and Drug Act of 1906
      a. Prohibited interstate commerce of adulterated or misbranded drugs
      b. Required labeling of selected dangerous and addictive substances
      c. Identified the United States Pharmacopeia and the National Formulary (USP/NF) as official standards for drugs

3. The Food, Drug and Cosmetic Act of 1938
    a. Required that firms prove evidence of safety to the FDA before marketing
    b. Placed drug advertising under the jurisdiction of the Federal Trade Commission
    c. Recognized the USP/NF as the official compendia of drug standards
4. The Durham-Humphrey Amendment of 1951: Amended the FD&C Act of 1938 to statutorily differentiate prescription and nonprescription drugs
5. The Kefauver-Harris Amendments of 1962
    a. Established the requirement that drug firms demonstrate efficacy as well as safety
    b. Established a statutory requirement to obtain informed consent for research subjects
    c. Authorized the FDA to regulate advertising of prescription drugs and establish good manufacturing practices
6. The Comprehensive Drug Abuse Prevention and Control Act of 1970 (i.e., the Controlled Substance Act): Authorized the DEA and FDA to regulate the manufacture, classification (schedule), importation, possession, use, and distribution of controlled substances
7. The Orphan Drug Act of 1983: Established grants, federal assistance for research, and tax incentives to develop drugs targeted to patient populations of fewer than 200,000 and for conditions where there is no expectation of cost recovery by the manufacturer
    a. Grants a period of market exclusivity to new medications (7 years) for these rare diseases
    b. This timeline is independent of patent life (20 years), which begins when a new molecule is invented, not when it gains approval.

Box 1. Suboxone Orphan Drug Status Timeline

- The first patent for Suboxone was filed in 1990.
- While it was being investigated under an IND, the manufacturer filed for orphan drug status in 1993. The application reflected that, despite the high rates of opioid addiction, fewer than 200,000 patients would be using the medication for opiate detoxification and maintenance. In addition, the application noted that market projections found no reasonable expectation that the costs of developing the drug would be recovered from sales. The drug was granted Orphan Drug Status in 1994.
- Suboxone was FDA approved in 2002, and the market exclusivity of 7 years began.
- Market exclusivity for this product lapsed in 2009. The FDA began accepting applications for generic products. The product patent for this formulation expired in 2010.
- The first generic formulations were brought to market in 2013.
- Controversy continues over the original estimates and approval of the product as an orphan drug.

8. The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act): Authorized the FDA to create an abbreviated regulatory pathway through the ANDA for generic drugs
    a. Grants a period of market exclusivity to new medications (4 or 5 years) or new indications (3 years) from approval until the acceptance of applications for generic drugs
    b. Grants the first approved generic drug 180 days of market exclusivity before other generic drugs may be approved
    c. Timeline independent of patent life
9. The Food and Drug Administration Act of 1988: Officially established the FDA as an agency in the DHHS
10. The Prescription Drug User Fee Act of 1992 (PDUFA)
    a. Requires drug, biologics, and medical device (Medical Device User Fee Amendments) manufacturers to pay fees for product applications, supplements, and other services
    b. Reauthorized every 5 years (1997, 2002, 2007, 2012, 2017)

11. The Dietary Supplement Health and Education Act of 1994: Allows nutritional supplements and vitamins to be regulated
12. The FDA Modernization Act of 1997
    a. Streamlines clinical research on drugs and devices
    b. Carries exclusivity provisions for pediatric drugs
    c. Authorizes the creation of a databank (ClinicalTrials.gov) to provide easy access to information on federally and privately supported clinical trials for a wide range of diseases and conditions
    d. Provides abstracts of clinical study protocols that investigators are required to submit
    e. Reauthorized PDUFA through 2002
13. The FDA Amendments Act (FDAAA) of 2007
    a. Statutory authority to require Risk Evaluation and Mitigation Strategies (REMS) for the safe use of medications (discussed later)
    b. Expanded the requirements for the types of drugs that must be registered on ClinicalTrials.gov; requires the submission of results for certain clinical trials
    c. Reauthorized the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, programs designed to encourage more research into, and more development of, treatments for children
    d. Reauthorized PDUFA through 2012
14. The Family Smoking Prevention and Tobacco Control Act of 2009: Gave the FDA authority to regulate tobacco products
15. The Biologics Price Competition and Innovation Act of 2009 (BPCI Act), passed as a provision within the ACA
    a. Established a regulatory approval pathway for biosimilars
    b. Set FDA-administered periods of regulatory exclusivity for certain brand-name drugs and follow-on products
    c. Created a patent dispute resolution procedure for use by brand-name biologics manufacturers
16. The Reducing Prescription Drug Shortages Executive Order, signed by President Barack Obama on October 31, 2011, requires the FDA to:
    a. Broaden the reporting of manufacturing discontinuances that may lead to shortages of drugs that are life supporting or life sustaining or that prevent debilitating disease
    b. Expedite regulatory reviews (including new drug suppliers, manufacturing sites, and manufacturing changes) to avoid or mitigate existing or potential drug shortages
    c. Communicate to the DOJ any evidence of or behaviors by market participants that have contributed to stockpiling or exorbitant pricing
17. The FDA Safety and Innovation Act of 2012 (reviewed earlier)
18. The DQSA of 2013 (reviewed earlier)

C. New Prescription Drug Approval Path
    1. The 1962 Kefauver-Harris Amendments, including a provision requiring manufacturers of drug products to establish a drug's effectiveness with "substantial evidence"
        a. It had been the FDA's position, on the basis of the language of the statute and the legislative history of the 1962 amendments, that Congress generally intended to require at least two adequate and well-controlled trials, each convincing on its own, to establish effectiveness.
        b. The United States Food and Drug Administration Modernization Act of 1997 stated that the agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence if the FDA determines that such data and evidence are sufficient to establish effectiveness.

2. Preclinical studies
    a. Laboratory and animal studies that assess safety and biologic activity of the IND in various model systems
    b. Toxicologic studies of the fetus in pregnant mice, rats, rabbits, or baboons. These studies may or may not translate to human beings and are the basis for pregnancy categorization
3. An INDA is drafted and submitted to the FDA. It must contain a general plan of investigation, drug information (i.e., chemistry, pharmacology, toxicology, pharmacokinetics, biologic disposition, laboratory and animal testing data, and existing human data), protocol, manufacturing, and control of the drug.
4. Phase I drug trial
    a. The initial introduction of an IND into humans typically involves 20–80 healthy volunteers after INDA approval.
    b. The goal is to garner information on the pharmacokinetic and pharmacodynamic properties and safety profile of the investigational drug to design a well-controlled and robust phase II trial.
5. Phase II drug trial
    a. Controlled clinical studies are conducted in no more than several hundred subjects
    b. The goal is to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under investigation and to determine the common short-term adverse effects and risks associated with the drug.
6. Phase III drug trial
    a. The investigational drug is administered to a range of several hundred to several thousand patient subjects in different clinical settings to confirm its safety, efficacy, and appropriate dosage.
    b. The goals are to gather necessary additional information about effectiveness and safety for evaluation of the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.
    c. This is the step before the sponsor's submission of an NDA to the FDA for approval to market the drug. Of note, the FDA may require a pediatric assessment if use in a substantial number of pediatric patients may be anticipated.
7. An NDA is submitted to the FDA and classified with a code that reflects both the type of drug being submitted and its intended uses. Not all phase III drugs are approved, and the FDA may impose a clinical hold at any stage.
8. Phase IV drug trial
    a. Also called postmarketing studies
    b. Verify effectiveness or focus treatment on special populations
    c. May be required by the FDA to identify additional information about the drug's risks, benefits, and optimal use

D. Generic Drug Approval
    1. A generic drug product is identical to an innovator drug product in bioequivalence and pharmaceutical equivalence as required by the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act). Demonstrations of bioequivalence indicate that there are no significant differences in the bioavailability (e.g., rate and extent of absorption of the active ingredient) under experimental conditions, such as that shown in vivo or in vitro studies.
        a. Pharmaceutical equivalents share the same active ingredient, dosage form and strength, route of administration, quality, and intended use (Box 2).

Box 2. Standards for Medications to Be Deemed Pharmaceutical Equivalents

Three criteria • Must contain the same active ingredient • Must be the same dosage form and route of administration • Must be of identical strength or concentration, quality, and purity
Differences allowed • Shape • Releasing mechanism • Labeling (limited differences) • Scoring • Excipients (colors, flavors, preservatives)

b. Therapeutic equivalence of generic drugs
   i. All approved multisource products are listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book). The therapeutic equivalence coding system (A or B rating), helps health care providers determine whether the FDA found a product to be therapeutically equivalent to other pharmaceutically equivalent products. Codes are assigned in accordance with data submitted in an ANDA to demonstrate bioequivalence.
      (a) A code: An approved generic product considered therapeutically equivalent to other pharmaceutical equivalents
      (b) B code: An approved generic product that is not considered therapeutically equivalent to other pharmaceutical equivalents
   ii. Therapeutic equivalents (rated A) may be substituted with the expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.
      (a) Criteria
         (1) Pharmaceutical equivalent
         (2) Demonstrates bioequivalence
      (b) Designates a brand-name drug or a generic drug as the reference-listed drug

2. An ANDA for a generic product must be submitted to CDER's Office of Generic Drugs.
   a. ANDAs generally do not require preclinical or clinical data; rather, they must demonstrate pharmaceutical equivalence and bioequivalence.
   b. Once an ANDA is submitted and approved, the applicant may manufacture and market the generic drug as a safe, effective, and low-cost option to the public.
3. An authorized generic is a drug that is produced by the brand company under the NDA but marketed as a generic. It is identical to the brand alternative in both active and inactive ingredients.
4. The federal FD&C Act establishes a 180-day exclusivity period after approval of an ANDA. During this period, the FDA may not approve other ANDAs for the same drug product. After 180 days, other generic manufacturers may submit ANDAs
5. In an at-risk launch of a generic, a generic drug manufacturer challenges the validity of the existing patent of a brand drug.

E. Biosimilars and Interchangeable Biologic Products
   1. A biologic product is a drug or vaccine that has been produced in living cells.
   2. The ACA amends the Public Health Service Act through part of the legislation known as the BPCI Act. This legislation created an abbreviated licensure pathway for biological products found to be biosimilar or interchangeable with an FDA-approved reference biological product after 12 years of patent exclusivity.

a. A biosimilar product is a biological product that is highly similar in safety and efficacy to an FDA-approved reference biological product, with only minor differences in clinically inactive components. There are several biosimilar products currently approved.
b. An interchangeable biological product is biosimilar to an FDA-approved reference biological product and meets additional standards. An interchangeable biological product may be substituted for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product. Because this interchange is also subject to state regulation, the statewide policy may override federal policy if it is more restrictive.
    i. The Biosimilar Implementation Committee, staffed by CDER, CBER, the Office of Chief Counsel, and the Office of the Commissioner, has developed several guidances for the industry that describe the current thinking relating to quality and scientific considerations in demonstrating biosimilarity, clinical pharmacology data required to demonstrate biosimilarity, reference product exclusivity for biological products, and nonproprietary naming of biological products. These guidances do not establish legally enforceable responsibilities of the FDA.
    ii. In May 2019, the FDA finalized a guidance document detailing the demonstration of interchangeability of biosimilars for industry. Despite this, no interchangeable biosimilars are currently approved because of the complexity and expense of the approval process.
c. Table 2 compares the regulatory pathway differences between traditional small molecules and biologics for FDA approval.

Table 2. Regulatory Approval Pathway Comparison for Small Molecule and Biologic Products

Product	Regulatory Pathway	Nonproprietary Name	Indications	Interchangeability	Clinical and Trial Data Requirement
Small Molecule (FD&C Act)	New drug application [505(b)1 and 2]	N/A; legend (brand) drug	N/A; legend (brand) drug	N/A; legend (brand) drug	Clinical data required; safety and efficacy data requirement
Generic small molecule	Abbreviated new drug application [505(j)]	Same as originator	Same as originator	Granted with initial approval (e.g., Orange Book rating)	Clinical data not required; bioequivalence data requirement
BPCI Act	Biologics license application [351(a)]	N/A; innovator (reference) drug	N/A; legend (brand) drug	N/A; legend (brand) drug	Clinical data required; purity, safety, and potency data requirement
Biosimilar	Biosimilar application [351(k)]	Same core name as reference plus four-letter suffix with at least three of the four letters being distinct	May or may not have all indications; extrapolation allowed	Not automatically granted at initial approval; requires additional review (e.g., Purple Book rating)	Clinical data required; abbreviated data requirement with purity, safety, and potency (i.e., totality of evidence)

N/A = not applicable

F. Medical Devices
1. An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory that is:
    a. Recognized in the official National Formulary (NF), or the USP, or any supplement to them
    b. Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in humans or other animals
    c. Intended to affect the structure or any function of the body of humans or other animals, does not achieve any of its primary intended purposes through chemical action within or on the body, and does not depend on being metabolized for the achievement of its intended purposes

2. Regulated by the Center for Devices and Radiological Health
    a. Categorized by the risks associated with the device into classes I–III. Class III devices, which carry the highest risk, are subject to the greatest regulatory control and must be approved by the FDA before marketing. A manufacturer of a class III medical device must submit a premarket approval application assuring the FDA of its safety and efficacy.
    b. If a medical device is essentially equivalent to an existing, legally marketed device, an investigational device exemption may be filed to allow for clinical study of its safety and effectiveness before a 510(k) is submitted for premarket notification.

G. Risk Evaluation and Mitigation Strategies (REMS)
1. The FDAAA of 2007 authorized the FDA to require REMS to ensure benefits outweigh risks before or after drug approval, if necessary. Examples of drug risks and possible actions include patient education on signs and symptoms, monitoring of laboratory values to help prevent serious adverse effects, the requirement of a negative pregnancy test before medications linked to serious birth defects are dispensed, and administration by a health care professional in the presence of high administration-related risk.
2. Is separate from the FDA's Risk Minimization Action Plans, which is a voluntary program for the industry for drugs that carry unusual risks but also unusual benefits
3. Requires that a drug be prescribed and dispensed with one of the following:
    a. Medication guide or patient package inserts
        i. Medication guides are not usually required as part of a REMS, however.
        ii. If the medication guide is listed as an Element To Assure Safe Use (ETASU), it must be provided in all settings (inpatient and outpatient).
    b. Communication plan to health care providers (for NDAs or biologics license applications only, not ANDAs)
    c. Elements to Assure Safe Use (ETASU) (Box 3)

Box 3. Risk Evaluation and Mitigation Strategies' Requirements of ETASU

ETASU may include one or more of the following:
- Health care providers who prescribe the drug have particular training or experience or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- Drug is dispensed only in certain health care settings
- Drug is dispensed to patients with evidence of safe use conditions, such as laboratory test results
- Each patient using the drug is subject to monitoring
- Each patient using the drug is enrolled in a registry

ETASU = Elements To Assure Safe Use

4. The FDA does not have the authority to impose penalties on pharmacies and pharmacists not in compliance with REMS requirements, but there may be legal implications, such as misbranding violations or civil liability issues.
5. Critical Path Initiative
    a. Created in response to a significant decline in NDAs, biologics license applications, and medical device applications because of the widening gap between basic science discovery and the challenging, inefficient, and costly development of medical products
    b. Prioritizes the most pressing developmental problems and identifies areas that provide the greatest opportunities for rapid improvement and public health benefit through three dimensions: safety assessment, evaluation of medical utility, and product industrialization

6. The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership that includes government agencies, industry representatives, patient advocacy groups, professional societies, investigator groups, academic institutions, and other stakeholders. It is aimed at improving the quality and efficiency of clinical trials.

Box 4. Buprenorphine/Naloxone REMS Program

REMS elements include:
- Medication guide
- ETASU
  - Documentation of several safe use conditions by the prescriber:
    - ✓ Patient meets diagnostic criteria
    - ✓ Risks have been explained
    - ✓ Safe storage has been reviewed
    - ✓ Limited quantity prescribed at first visit
  - REMS Instruction Letter to Prescribers mailed annually to all physicians certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 and all retail pharmacies authorized by the DEA to handle Schedule 3 controlled substances by manufacturer
  - Documented patient monitoring:
    - ✓ Regular visits
    - ✓ Adherence assessments
    - ✓ Appropriate prescribing
    - ✓ Psychosocial support assessment
    - ✓ Progress toward treatment goals

DEA = Drug Enforcement Administration.

V. ACCREDITING ORGANIZATIONS AND QUALITY IMPROVEMENT EFFORTS

A. Accreditation is often necessary for a variety of healthcare organizations to receive payment through programs, including federally funded Medicare and Medicaid programs.

B. Accreditation: The Joint Commission
   1. Independent not-for-profit organization that sets standards for the accreditation of health care facilities through its mission "to continuously improve health care for the public, in collaboration with other stakeholders, by evaluating health care organizations and inspiring them to excel in providing safe and effective care of the highest quality and value"
   2. Accredits and certifies more than 22,000 health care organizations in the United States. Accreditation is reassessed every 3 years on the basis of adherence to hospital standards, as assessed during on-site surveys and quality reporting of performance indicators.
      a. Standards address performance in functional areas of patient rights, patient treatment, medication safety, and infection control. National Patient Safety Goals were established to help accredited organizations address specific areas of concern in patient safety. Goals differ by health care setting and can change on the basis of recommendations from the Patient Safety Advisory Group.
      b. In on-site surveys, which are unannounced, tracer methodology is used to evaluate a patient's medical record as a road map through a health care organization to evaluate its compliance with standards and systems to provide care and services. First-generation tracers follow a patient through care areas, whereas second-generation tracers focus on major organizational areas, such as high-alert medications and medication shortages.

c. Performance measurement: ORYX is a Joint Commission initiative to integrate outcomes with accountability in core measures pertaining to perinatal care, management of venous thromboembolism, substance abuse, tobacco treatment, emergency department care, and immunization practices, among others, in its accreditation process.
   i. Included accountability measures and processes are those that result in the greatest improvement in patient outcomes as identified by the Joint Commission. These measures and processes must be of sound scientific evidence, be in proximity between process and outcome, accurately measure the process, and minimize adverse effects without inducing unintended consequences. Measures are updated semiannually.
   ii. National Hospital Quality Measures include common standardized measures between The Joint Commission and CMS, designed to share a single set of documentation (Box 5).

Box 5. National Hospital Inpatient Quality Measure for Substance Abuse (SUB)-3

Measure: Alcohol and Other Drug Use Disorder Treatment Provided or Offered at Discharge
Type of Measure: Process
Description: Patients who are identified with alcohol or drug use disorder who receive or refuse at discharge a prescription for FDA-approved medications for alcohol or drug use disorder, OR who receive or refuse a referral for addiction treatment
Rationale: Excessive alcohol and substance abuse negatively affects health and society; brief interventions have been found improve health and reduce costs

   iii. National Quality Measures contain measures not common to CMS.
   iv. The Targeted Solutions Tool, created by the Joint Commission Center for Transforming Healthcare, provides a process for accredited hospitals to measure performance, identify barriers to excellent performance, and implement proven solutions.

C. Accreditation and Certification: The National Committee for Quality Assurance (NCQA)
   1. Private, not-for-profit organization with a mission to improve the quality of health care through measurement, transparency, and accountability
   2. Responsible for the development and maintenance of the HEDIS
      a. Consists of more than 90 measures across six domains of care that health plans use to measure performance and focus improvement efforts. Domains include effectiveness of care, access to/availability of care, experience of care, use and risk-adjusted use, health plan descriptive information, and measures collected using electronic clinical data systems.
      b. Several measures are included in CMS's Quality Rating System for health plans participating in federally facilitated marketplaces for consumers to view.
   3. Voluntary accreditation programs, certification programs, physician recognition programs, and distinctions are directed at health plans (e.g., health maintenance organizations, preferred provider organizations, and consumer-directed health plans), physician networks, medical groups, and individual physicians.
      a. Notably certifies and recognizes PCMHs
      b. Assessments may include on-site clinical and administrative processes, through data collection for the HEDIS, and measuring member satisfaction through the Consumer Assessment of Healthcare Providers and Systems survey.
   4. The Quality Compass: A comparison tool that allows users to view measure results and benchmark information. The tool ranks health plans using the HEDIS measures.

5. Public reporting: "The State of Health Care Quality," which is an annual overall assessment of the performance of the American health care system; "America's Best Health Plans," in collaboration with *U.S. News & World Report;* and the online Health Plan Report Card with a searchable database detailing health plans' accreditation and performance ratings

D. The Center for Pharmacy Practice Accreditation: Established by the American Pharmacists Association, the National Association of Boards of Pharmacy, and American Society of Health-System Pharmacists, it offers voluntary accreditation for pharmacy practice sites on the basis of adherence to comprehensive and patient-centered medication use performance measures. Accreditation includes community, specialty, and telehealth pharmacy practice programs.

E. Quality Improvement Efforts
   1. Development of the National Quality Strategy (NQS)
      a. The Clinton administration formed the President's Advisory Commission on Consumer Protection and Quality in the Healthcare Industry, which recommended steps to provide a "national commitment to improving healthcare quality." This led to the formation of the NQF in 1999 (described below).
      b. Medicare Improvements for Patients and Providers Act of 2008: The DHHS entered into a contract with the NQF to establish a portfolio of quality and efficiency measures for use in reporting on and improving health care quality for the federal government to determine a return on investment in health care spending. This work, in combination with the Institute for Healthcare Improvement's Triple Aim and the Institute of Medicine's 6 Aims, laid the foundation for the development of a NQS.
      c. The ACA officially charged DHHS with developing a NQS. The NQF led the development of the National Priorities Partnership of 52 partner organizations to develop the NQS. The NQS, published in 2011, includes three aims and six priorities for the quality improvement of health care.
   2. Strategies to enhance health care quality
      a. Value-based purchasing: rewarding of high-quality care by such groups as CMS, employer purchasers, health plans and consumers; achieved by measuring and reporting on quality measures
      b. Outcomes-based performance: payment and reimbursement based on the achievement of a specific outcome rather than a single action or service
      c. Publicly reporting data: to drive systems to benchmark and achieve quality care
   3. The National Quality Forum (NQF)
      a. Nonprofit organization comprising stakeholders from consumer organizations, public and private purchasers, physicians, nurses, accrediting and certifying bodies, supporting industries, and health care research and quality improvement organizations
      b. Aimed at improving quality through a three-part mission:
         i. Building consensus on national priorities and goals for performance improvement and working in partnership to achieve them
            (a) As a result of the Medicare Improvements for Patients and Providers Act, the NQF identified priorities for health care performance measurement based on evidence related to 20 high-priority conditions.
            (b) The conditions were identified by CMS to account for more than 95% of their costs.
         ii. Endorsing national consensus standards for measuring and publicly reporting on performance; assessing evidence to support and endorse quality measures proposed by other organizations (NCQA, American Medical Association, etc.) through a transparent, consensus-based practice
         iii. Promoting the attainment of national goals through education and outreach programs

4. The Agency for Healthcare Research and Quality (AHRQ)
    a. The AHRQ is a DHHS agency that supports research to help people make informed decisions and improves the quality of health care services through its mission to improve the quality, safety, and effectiveness of health care for all Americans
    b. Health service research provides clinical, health care system, and public policy decision-makers evidence-based information on health outcomes, quality, cost, use, and access to improve the quality of health care services.
    c. The Consumer Assessment of Healthcare Providers and Systems (CAHPS) supports and promotes the assessment of consumer experiences with health care. Its surveys assess the patient experience with health care services at multiple levels of delivery (e.g., health plans, hospitals [HCAHPS] and dialysis centers). The CAHPS is used in a variety of assessments, including those by the NCQA.
    d. Hosts the National Quality Measures Clearinghouse, which details summaries of evidence-based quality measures and measure sets used in a variety of settings, endorsed by various organizations, and used in several initiatives, including CMS initiatives
    e. Funding opportunities, toolkits, and resources are available for researchers, clinicians, policy makers, and consumers.
5. The Patient-Centered Outcomes Research Institute (PCORI): Nonprofit authorized by Congress in 2010 that is charged with improving the quality and relevance of evidence available to help patients, caregivers, clinicians, employers, insurers, and policy makers form health decisions through the support and funding of comparative clinical effectiveness research (CER)
6. The Pharmacy Quality Alliance (PQA)
    a. The mission of the PQA is to improve the quality of medication use across health care settings.
    b. Develops medication-related performance measures—including adherence, medication use in older adults, opioid use, and medication therapy management, among others—through a collaborative process with key stakeholders
7. Centers for Medicare and Medicaid Services (CMS) Initiatives
    a. Hospital Value-Based Purchasing Program was established by the ACA in 2010 and uses quality measures endorsed by the NQF as well as the AHRQ's HCAHPS to establish and apply criteria for reimbursement and incentive payments. Performance data are public on the Hospital Compare website.
    b. Physician Quality Reporting System (QRS) ties quality measures to physician reimbursement and makes some data public on the Physician Compare website. Under MACRA, this was combined into the MIPS program.
    c. Health Insurance Marketplace Quality Rating System (QRS) aims to:
        i. Provide useful information to consumers using the Health Insurance Marketplace. Plans are required to display their QRS star ratings (5-star scale) on their websites, and ratings will be displayed through all exchanges. These ratings incorporate quality measures such as the NCQA's HEDIS and several PQA measures.
        ii. Provide actionable information that plans can use for performance improvement
            (a) The Quality Bonus Payment Demonstration Project was designed to drive quality improvement by extending bonus payments for improvements to low-performing plans.
            (b) EQuIPP is a performance information management system that makes performance data available to both health plans and pharmacy organizations. It creates a potential opportunity for community pharmacies to improve plan ratings. For example, the completion rate of comprehensive medication reviews completed for eligible patients helps to guide a plan's rating. Pharmacists are an integral part in completing this measure.
        iii. Facilitate oversight of qualified plans

8. The Leapfrog Group is a voluntary program that works with employers to enable and direct purchasing power toward health care decisions focused on safety, quality, and value. It compares hospital performance on the metrics most important to consumers and purchasers of care. A Hospital Safety Grade of A, B, C, D, or F has been applied to more than 2500 hospitals on the basis of prevention of errors, accidents, injuries, and infections.

VI. INSTITUTIONAL MEDICATION USE POLICY CONSIDERATIONS

A. Formulary Management
   1. Basics
      a. Formulary management is an ongoing process by which a health care organization establishes medication use policies on drugs, therapies, and drug-related products that are evidence based and cost effective in certain patient populations.
      b. The Joint Commission Medication Management Standards chapter of the Hospital and Hospital Clinics manual requires the hospital to develop and approve criteria for selecting medications that include indications for use, effectiveness, drug interactions, potential for errors and abuse, adverse drug events, sentinel event advisories, populations served, other risks, and costs.
      c. The CMS CoP require that medical staff establish a formulary system.
      d. A pharmacy and therapeutics (P&T) committee develops consensus on medication use policies and formulary management.
      e. Evidence-based evaluation of medications for inclusion on a formulary includes a drug use review or drug use evaluation (DUE) and will be affected by CER.
   2. Definitions
      a. Formulary: A continually updated list of medications and related information, developed with the clinical judgment of pharmacists, physicians, and other experts in the diagnosis and treatment of disease and promotion of health within hospitals, health plans, and health care systems
      b. DUE: Process used to assess the appropriateness of drug therapy in which data on drug use in a given health care environment are compared with predetermined criteria and standards
      c. Medication use evaluation (MUE): Performance improvement method that focuses on evaluating and improving medication-use processes related to prescribing, medication preparation, dispensing, administering, and monitoring. Medication use evaluations are often also tied to cost savings.
   3. Formulary management strategies
      a. Preferential use of generic drugs
      b. Formulary exclusion: Process of limiting medications from the formulary (called non-formulary or non-preferred medications)
         i. Open formulary: Non-formulary or non-preferred medications may be covered at variable levels of cost within a health plan.
         ii. Closed formulary: Non-formulary or non-preferred medications are not covered within a health plan unless under an exception where medically appropriate.
         iii. Formulary restrictions: Restricting prescriptive authority to a particular service or disease state (Box 6)

Box 6. Example: Suboxone (Buprenorphine/Naloxone) Sublingual Film Formulary Criteria for Use

Health systems may wish to restrict the use of agents that are deemed high risk, high cost, or as needing special monitoring (e.g., Suboxone)
Criteria for use may include: • Patient inclusion: Patients meeting diagnostic criteria for opioid dependence/use disorder needing opioid agonist therapy • Provider inclusion: Authorized to prescribe Suboxone by meeting all requirements for a waiver specified by the Drug Addiction Treatment Act (DATA) 2000 as codified at 21 U.S.C. 823(g), who has experience in addiction management; assurance of the availability of necessary treatment resources must be completed by the physician before prescribing. The waiver is sometimes called the "X waiver" because the DEA number assigned begins with an "X" • Considerations for use: ◦ Alternative first-line therapies for opioid dependence include methadone, though this agent is not available for office-based opioid treatment ◦ Consider the potential for corrected QT interval prolongation in unstable cardiac disease or low potassium concentrations ◦ Consider the potential for drug interactions with CYP3A4 inhibitors or inducers and with central nervous system depressants ◦ Patients will need monitoring for several hours after administration of induction doses ◦ Patients should be seen weekly for the first 2 weeks of therapy and then at least monthly for the next 3 months ◦ Therapy should be discontinued if the patient is found to misuse, abuse, or divert the medication; to be noncompliant with therapy; or to be unresponsive to therapy • System responsibilities: ◦ Procedures to verify provider authorization and to restrict use to authorized prescribers must be in place ◦ Quantity limits may be imposed such that enough medication is dispensed to last only until the next scheduled appointment

CYP3A4 = cytochrome P450 3A4 isozyme.

iv. Therapeutic interchange: Authorized exchange of therapeutic alternatives through written guidelines, policies, or protocols within a formulary system

v. Guided-use requirements: Include use criteria, clinical practice guidelines, and operating procedures

vi. MUE: MUEs differ from DUEs in that MUEs emphasize improving patient outcomes using a process that identifies, resolves, and prevents medication-related problems (actual or potential). An MUE may be applied more broadly than a single medication, such as to a therapeutic class, disease state, medication use process, or specific outcomes. Steps in conducting MUEs include:
   (a) Establishing and implementing criteria, guidelines, treatment protocols, and standards of care for medications and medication use policies
   (b) Selecting medications for MUE on the basis of adverse medication events or risk of events, signs of treatment failures, expense of medication, patient population, or disease state
   (c) Identifying data points and collecting data
   (d) Evaluating adherence to criteria, guidelines, treatment protocols, and standards of care for medications and medication use policies
   (e) Interpreting and reporting MUE findings
   (f) Identifying and implementing improvement strategies in the medication-use process

B. Medication Safety Monitoring and Reporting
   1. Differentiation between medication errors, adverse events, and adverse reactions is critical to the evaluation and risk minimization process. Table 3 outlines the differences between medication errors, adverse drug events, and adverse drug reactions, or non-preventable adverse drug events.

Table 3. Differences between Medication Errors, Adverse Drug Events, and Adverse Drug Reactions

Term	Definition	Example
Medication error	Any error occurring in the medication process (ordering, transcribing, dispensing, administering, and monitoring) Some medication errors cause injury (result in an ADE); others do not	Order filled for the wrong patient
Near miss	Medication errors that are intercepted and stopped before they occur	Overdosage of a medication that was intercepted before patient administration
Adverse drug event	Injury resulting from the use of a drug that includes harm caused by the drug (ADRs and overdoses) and harm from using the drug, including dose reductions and discontinuations	Hemorrhage from heparin
Preventable adverse drug event	ADE that was preventable by modification of behavior, practice, technique, or care. Results from any medication error that reaches the patient and causes harm. Includes drug interactions	Overdosage of a medication that resulted in a hospitalization
Adverse drug reaction	Non-preventable injury caused by the drug at normal doses and with normal use; not a result of a medication error	Allergic reaction in a person with no known allergies

   2. Medication errors
      a. In 1999, the Institute of Medicine (IOM) released a report titled "To Err Is Human," which stated that medical errors claim as many as 98,000 lives a year. The 2004 IOM report "Patient Safety: Achieving a New Standard for Care" revealed the high incidence of adverse events occurring in hospitals.
      b. The Patient Safety and Quality Improvement Act of 2005 (Patient Safety Act [PSA]) and the Patient Safety and Quality Improvement Final Rule (Patient Safety Rule) were a congressional response to these reports. The Patient Safety Rule requires the AHRQ to administer a Network of Patient Safety Databases to assess national de-identified patient safety events.
         i. Encourages health care providers and organizations to voluntarily report and share patient safety information without fear of legal action
         ii. Authorizes the creation of patient safety organizations (PSOs)
            (a) Private or public entities, profit or not-for-profit entities, provider entities such as a health system, or other entities
            (b) PSOs provide a secure mechanism for the collection, aggregation, and analysis of data to identify and reduce risks and hazards that may occur with patient care delivery.
         iii. The AHRQ created the Patient Safety Organization Privacy Protection Center to support the implementation of the Patient Safety Act. The Privacy Protection Center provides technical assistance to PSOs to ensure that data on patient safety events submitted to the Network of Patient Safety Databases are non-identifiable. PSOs not listed with AHRQ are not recognized under the PSA.

(a) Data are submitted to PSOs through Common Formats, developed by AHRQ for acute care hospitals and skilled nursing facilities. Common Formats provide a systematic process for reporting adverse events, near misses, and unsafe conditions, and they allow a hospital to report harm from all causes.
(b) The NQF leads the public review and lends expert opinion regarding the Common Formats.
(c) In March 2013, CMS communicated that although the use of Common Formats is not required for CoP for Quality Assessment and Performance Improvement surveys, hospitals that use them will be in a better position to meet Quality Assessment and Performance Improvement requirements.
(d) CMS surveyors were also encouraged to become familiar with Common Formats.

c. The ACA charges PSOs to assist health systems with a high rate of risk-adjusted readmission rates to decrease readmission rates and improve transitions of care.
   i. The Institute for Safe Medication Practices was begun in 1975 to promote medication error prevention and initiated a voluntary practitioner error-reporting program. The institute is now a nonprofit PSO that publishes four medication safety alert newsletters for acute care settings, ambulatory care settings, nurses, and medications.
   ii. Vizient, formerly known as the University HealthSystem Consortium (UHC), is an alliance of academic medical centers and affiliated hospitals that is named as an AHRQ-listed patient safety organization under the UHC Performance Improvement PSO. It offers the UHC Patient Safety Net, a web-based inpatient and outpatient safety event-reporting system that consolidates and aggregates data for specific event types and offers best practices and policies to address common systemic areas for improvement.

3. Adverse events
   a. Grades of certainty criteria, including certainty/definite, probable/likely, possible, and unlikely/doubtful, determine whether an adverse event is caused by a medication and can be assessed using tools such as the Naranjo Adverse Drug Reaction (ADR) Scale or the World Health Organization (WHO)-Uppsala Monitoring Centre (UMC) Causality Assessment.
   b. Adverse drug events should be reported to the FDA Adverse Event Reporting System (FAERS), a database with more than 400 million adverse event and medication error reports.
      i. MedWatch Form FDA 3500 is for voluntary reporting of a serious adverse event, product quality problem, or product use error with an FDA-regulated drug, biologic, medical device, or dietary supplement by health care professionals. This includes errors in medication use because of ambiguities in directions, packaging, and product name, as well as product quality issues. These issues should be reported even when it is unclear whether the medication was the cause of the event. The HIPAA Privacy Rule specifically permits health care professionals to disclose PHI for public health purposes.
      ii. MedWatch Form FDA 3500A is for regulated industry following investigational new drug (IND) and biologic regulations and user facilities such as hospitals and nursing homes.
      iii. MedWatch Form FDA 3500B is available for consumer reporting.
      iv. Submitted events are evaluated by CDER and monitored by CBER.
      v. Vaccine-related adverse effects, veterinary medicine product adverse events, and suspected unlawful internet sales of medical products should not be reported to MedWatch.
   c. The Vaccine Adverse Event Reporting System is a national postmarketing vaccine safety surveillance program managed by the CDC and the FDA for vaccine-related adverse events to be reported, analyzed, and made available to the public. The National Childhood Vaccine Injury Act of 1986 requires health care professionals and vaccine manufacturers to report to DHHS specific adverse events that occur after the administration of routinely recommended vaccines.

d. The FDA's Sentinel Initiative was implemented as a result of the FDAAA of 2007 to proactively monitor the safety of FDA-regulated products such as drugs, vaccines, and medical devices. It is being implemented in stages to complement existing reporting systems, and it will have functionality to query electronic medical records, administrative and insurance claims, and registries.

4. Workplace safety: Occupational Safety and Health Administration
   a. Ensures safe and healthful working conditions for employees
   b. Is part of the U.S. Department of Labor
   c. Was granted regulatory authority through the Occupational Safety and Health Act of 1970
5. Safety of compounded products
   a. The USP develops standards, enforceable by the FDA, for the identity, strength, quality, and purity of medications and dietary supplements, including compounded products.
   b. Pharmacies may be subject to inspection against these standards by boards of pharmacy, the FDA, The Joint Commission, and other entities.
   c. The USP General Chapters are as follows: Required (numbered below <1000>), Informational (numbered above <1000>), and Specific for dietary supplements (numbered above <2000>). USP is a standard-setting organization; the USP standards are enforced by federal and state regulators and accreditation organizations (e.g., The Joint Commission, DNV Healthcare). The chapters pertaining to compounding include the following:
      i. USP 795: Pharmaceutical Compounding– Nonsterile Preparations (CNSPs)
      ii. USP 797 Pharmaceutical Compounding for Sterile Preparations (CSPs)
         (a) Because of deaths associated with microorganism contamination, CSPs have been under scrutiny. In October 2015, CMS issued a revision to its Pharmaceutical Services Conditions of Participation State Operations Manual aligning its standards of practice for drug compounding with USP General Chapters requirements, particularly for CSPs.
         (b) An area of interest for organizations is beyond-use dating (BUD) and sterility for CSPs. According to USP 797, BUD is based on several factors, including the preparation environment, aseptic processing and sterilization, components, sterility testing, and storage conditions. Preparations mixed in a <797>-compliant clean room may use the full BUDs listed in <797>, but those made in less-controlled areas must be assigned a shorter BUD.
      iii. USP 800: Hazardous Drugs: Handling in Healthcare Settings describes practice and quality standards to ensure a quality environment and protection of health care workers and patients when hazardous drugs (HDs) are handled. Handling HDs includes, but is not limited to, the receipt, storage, compounding, dispensing, administration, and disposal of sterile and nonsterile products and preparations. This chapter applies to all health care personnel who handle HD preparations and all entities that store, prepare, transport, or administer HDs.
      iv. USP 825: Radiopharmaceuticals describes the processes needed for handling radiopharmaceuticals in nuclear pharmacies and nuclear medicine departments.
      v. Chapters are revised from time to time. Requirements (*shall* and *must* statements) and recommendations (*should* statements) of the most current chapter must be used.
6. Supporting Patient Access to Medications
   a. Options exist for supporting and supplementing patient access to medications. Pharmacists are a conduit for linking patients to medication discount and prescription assistance programs.
   b. The 340B Drug Pricing Program, authorized through the Medicaid Drug Rebate Program in 1990 and expanded by the ACA in 2010, allows specific categories of safety-net providers to become established entities and procure outpatient prescription drugs at discounted prices. The 16 categories of covered entities use the discounts to expand or develop new services.
      i. Eligibility is defined at the level of the health care facility and not the individual; however, the HRSA's Office of Pharmacy Affairs states that only patients with an established relationship with the covered entity are eligible to receive 340B purchased drugs.

ii. Covered entities can procure drugs at 340B prices and distribute them in the following ways:
(a) Through in-house pharmacies or to an outpatient clinic for direct administration to patients
(b) Distribution to the patient from a contracted pharmacy
iii. In January 2018 Medicare lowered reimbursements to 340B program providers, sparking controversy.
iv. Numerous bills have been proposed to alter various components of the current 340B program.

c. Patient and prescription assistance programs are operated by drug manufacturers to provide free medications to patients who cannot afford them.

A. History
1. The National Research Act of 1974 created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, partly in response to the Tuskegee Syphilis Study. This group issued the 1978 Belmont Report, summarizing the ethical principles and guidelines for conducting human subjects research.
2. As a result of the Belmont Report, the Federal Policy for the Protection of Human Subjects (Common Rule) was published in 1991.

VII. INVESTIGATIONAL DRUG SERVICE

A. The ASHP Guidelines for the Management of Investigational Drug Products released in 2018 strongly supports pharmacists' management of the control and distribution of drug products used in clinical research.

B. The purpose of an IDS is to procure, manage, prepare, dispense, and dispose of investigational drugs in accordance with protocol and in compliance with the state and federal requirements that govern investigational drug activities.

C. Drugs, as defined by the FD&C Act, are "(A) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and (B) articles (other than food) intended to affect the structure or any function of the body of man or other animals" (FD&C Act, sec. 201[g][1]). An investigational drug is a chemical or biologic substance that has been tested in a laboratory and been approved by the FDA for testing in human subjects. An investigational (also referred to as experimental) drug may be:
1. A new chemical or compound that has not been approved by the FDA for general use
2. An approved drug undergoing further investigation for an approved or unapproved indication, dose, dosage form, or administration schedule or under an INDA in a controlled, randomized, or blinded clinical trial

D. In addition to the regulations outlined by the Office for Human Research Protections (Common Rule) and the FDA to conduct research in accordance with the principles of good clinical practice and human subject protection, an IDS has federal and state requirements.
1. The Joint Commission standards require policies for the use of investigational drugs that specifically address their storage, dispensing, labeling, and distribution.
2. The U.S. EPA and the Occupational Safety and Health Administration regulate the disposal of investigational drugs.
3. ASHP provides practice standards.

4. The local IRB has its own requirements.
5. State-specific laws may vary.

E. Study-specific notebook: The notebook is maintained where study drugs are stored. It contains the files and contents listed in Table 4.

Table 4. Example of Documents Stored in Study-Specific Notebooks Maintained by an Investigational Drug Service

File Section	Contents
Protocol	Copy of the research protocol
Drug information	Investigator's brochure, drug data sheet, package inserts (if commercially available)
Pharmacy procedures	Study-specific pharmacy procedure information
Logs, forms, and labels	Study-specific materials
Procurement details	Receipt and disposition records
Correspondence	Communication records
Computer matters	Copies of order entry codes
Billing	Financial agreements with investigator
IRB	IRB submission application, approval, and consent forms
Miscellaneous	Miscellaneous documentation
Master patient log	Record of patients enrolled
Drug accountability records	Data accountability record for each drug, dosage form, package size, and strength

IRB = institutional review board

F. An investigational drug pharmacist's duties may include:
1. Participating on an IRB as a voting member
2. Maintaining a working relationship with the IRB, P&T committee, principal investigators, and the pharmacy department
3. Reviewing new and existing investigational drug study protocols
4. Meeting with investigators, study monitors, and other study personnel responsible for coordinating the logistics of a clinical trial
5. Receiving, organizing, and maintaining the contents of study notebooks
6. Providing randomization, blinding, or control functions of a clinical trial
7. Conducting the training of IDS staff and personnel regarding investigational protocols and study drug procedures

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ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A
The 21st Century Cures Act authorized an increase in funding to be provided to the NIH. This funding, however, is discretionary and will need annual congressional approval through the Appropriations committees in the House and Senate, making Answer A correct. The two Appropriations committees, responsible for funding agencies of the U.S. government, include several subcommittees, among them the subcommittees on Labor, Health and Human Services, and Education and Related Agencies. The House Energy & Commerce and Senate HELP committees are responsible for regulations governing public welfare, including the DHHS, NIH, FDA, CDC, and AHRQ, making Answers B & C incorrect. The House Ways & Means and Senate Finance committees are responsible for tax legislation affecting Medicare/Medicaid and CHIP, making Answer D incorrect.

2. Answer: C
Research involving human subjects is regulated by the Office for Human Protections within DHHS, making Answer A incorrect. HIPAA provisions to protect protected health information are enforced by the Office for Civil Rights within DHHS, making Answer B incorrect. The diversion of controlled substances and monitored chemicals is the responsibility of the Drug Enforcement Agency, an executive agency under the Department of Justice, making Answer C correct. The U.S. Food and Drug Administration's Office of Regulatory Affairs, which inspects regulated products and manufacturers, falls under DHHS, making Answer D incorrect.

3. Answer: C
Traditional compounders fall under Section 503A of the DQSA and outsourcing facilities under Section 503B. Outsourcing facilities, but not individual compounders, must register with the FDA, are subject to inspection by the FDA, and must report on compounded products and bulk ingredients to the secretary every 6 months, making Answer A incorrect. Similarly, outsourcing facilities, but not traditional compounders, must follow good manufacturing practices for compounding and are exempt from track-and-trace requirements, making Answers B and C incorrect. Traditional compounders must follow USP guidance for compounding, must compound products for an identified individual patient, and must follow track-and-trace requirements, making Answer C correct and, furthermore, making Answer D incorrect.

4. Answer: A
The Safe and Secure Drug Disposal Act of 2010 authorized the DEA, not DHHS, to promulgate rules for patient disposal of unused controlled substances and controlled substance disposal by long-term care facilities, making Answer B incorrect. It authorizes manufacturers, distributors, reverse distributors, narcotic treatment programs, hospitals and clinics with on-site pharmacies, and retail pharmacies, including long-term care facilities and specialty pharmacies, to become collectors but does not require it, making Answer D incorrect and Answer A correct. Although specified entities are permitted to reverse distribute in certain circumstances, they need not be registered as reverse distributors, making Answer C incorrect.

5. Answer: A
The Medicare Access and CHIP Reauthorization Act (MACRA) of 2015 represents a shift in reimbursement from fee-for-service to pay-for-performance or pay-for-value. It created two primary reimbursement programs: alternative payment models (APMs) and a merit-based incentive payment system (MIPS) for eligible providers, making Answer A correct. This legislation also replaces three existing value-based payment adjustments: the Physician Quality Reporting System, the Value-Based Payment Modifier, and the EHR incentive program ("meaningful use"), making Answer B incorrect, and combines them into MIPS. The American Recovery and Reinvestment Act of 2009 includes the Health Information Technology for Economic and Clinical Health (HITECH) Act, which established the program now known as "meaningful use." The Affordable Care Act created an optional Medicaid State Plan benefit that allows states to establish Health Homes to provide comprehensive care for Medicaid patients with chronic conditions and created the CMS Innovation Center to develop new care models, making Answers C and D incorrect.

6. Answer: B

The INDA is used for a new drug, a new indication, or off-label use that will be used in a clinical investigation's preclinical development for that new drug to be distributed across state lines before undergoing full FDA review. An INDA is drafted and submitted to the FDA after a preclinical study, before a phase I clinical trial, when the IND is first introduced into human subjects, making Answer B correct and Answers A, C, and D incorrect. The application must contain a general plan of investigation, drug information (i.e., chemistry, pharmacology, toxicology, pharmacokinetics, biologic disposition, laboratory and animal testing data, and existing human data), protocol, and manufacturing and control of the drug. An NDA is submitted after phase III studies, before market approval, making Answer D incorrect.

7. Answer: D

ANDAs, not NDAs, for generic drugs are submitted to the FDA's Center for Drug Evaluation and Research after 3–5 years of market exclusivity, making Answer A incorrect. Drug manufacturers are required to demonstrate bioequivalence equivalence, but not therapeutic equivalence, in their ANDA for a generic drug, as outlined in the Hatch-Waxman Act, making Answer B incorrect. Once the ANDA has been approved, the generic and brand manufacturer retains a 180-day exclusivity period during which the FDA may not approve other ANDAs for the same drug product, making Answer C incorrect. During this time, the brand manufacturer is producing an authorized generic. An authorized generic is produced by the brand company under the NDA but marketed as a generic, making Answer D correct. It is identical to the brand-name drug except for labeling, packaging, product/labeler code, trade name, or trademark.

8. Answer: D

Products with an A rating are both pharmaceutical equivalents and bioequivalents and can be interchanged, making Answer A incorrect. Products with a B rating are pharmaceutical equivalents only and cannot be interchanged, making Answer C incorrect. Interchangeable products must also be pharmaceutical equivalents and may therefore vary in their release mechanism or excipients but not in their dosage form or route of administration, making Answer B incorrect and Answer D correct.

9. Answer: D

The FDA requires manufacturers, packers, and distributors of marketed prescription drug products to establish and maintain records and to make reports to the FDA of all serious, unexpected adverse drug experiences associated with the use of their drug products. Form FDA 3500 is for voluntary reporting by health care professionals, consumers, and patients, whereas 3500A is the form that must be submitted by IND reporters, manufacturers, distributors, importers, and facility personnel, making Answer D correct and Answer A incorrect. Manufacturers, packers, and distributors should not include the names and addresses of individual patients. However, health care providers may continue to make adverse event reports under the HIPAA Privacy Rule. The HIPAA Privacy Rule is not intended to disrupt or discourage adverse event reporting in any way. In fact, the Privacy Rule specifically permits covered entities (e.g., pharmacists, physicians, hospitals) to report adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products, both to the manufacturers and directly to the FDA. As an explanation, the following statement has been provided: "The HIPAA Privacy Rule recognizes the legitimate need for public health authorities and others responsible for ensuring public health and safety to have access to PHI to carry out their public health mission. The rule also recognizes that public health reports made by covered entities are an important means of identifying threats to the health and safety of the public at large, as well as individuals. Accordingly, the rule permits covered entities to disclose PHI without authorization for specified public health purposes." However, names of patients, individual reporters, health care professionals, hospitals, and geographic identifiers in adverse drug experience reports are not releasable to the public under the FDA's public information regulations, making Answer C incorrect. Answer B is incorrect because consumers and patients should complete Form 3500B.

10. Answer: C

A preventable ADE, by definition, is a medication error that occurs and reaches the patient to cause harm because of a breach of standard professional behavior or practice. The drug interaction between rivaroxaban and rifampin is a known interaction that is described in the prescribing information. This is a medication error, and

the stroke is the harm (Answer C is correct). Although this case of rifampin/rivaroxaban drug interaction–induced stroke is an ADE, a preventable ADE best describes this case (Answer D is incorrect). In general, ADRs and side effects are synonymous, and a stroke resulting from a rifampin/rivaroxaban drug interaction is an ADR; however, a preventable ADE best describes this case (Answers A and B are incorrect).

11. Answer: C

The NCQA, not the Joint Commission, is responsible for developing and maintaining the HEDIS that health plans use to measure performance and focus improvement efforts, making Answer A incorrect. The Agency for Healthcare Research and Quality developed the HCAHPS survey, which measures the consumer experience with health care and can be used to make quality assessments for programs such as value-based purchasing. The PCORI supports and funds comparative clinical effectiveness research, making Answer B incorrect. The Joint Commission is responsible for developing and maintaining the National Hospital Quality Measures as a part of its ORYX initiative to integrate outcomes and accountability into core measures, making Answer D incorrect. The NQF endorses national consensus standards for measuring and publicly reporting on performance, making Answer C correct.

Biostatistics: A Refresher

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Learning Objectives

1. Describe differences between descriptive and inferential statistics.
2. Identify different types of data (nominal, ordinal, continuous [ratio and interval]) to determine an appropriate type of statistical test on the basis of the sample distribution, data type, and study design.
3. Describe strengths and limitations of different types of measures of central tendency (mean, median, and mode) and data spread (standard deviation, standard error of the mean, range, and interquartile range).
4. Describe the concepts of normal distribution and the associated parameters that describe the distribution.
5. Describe hypothesis testing, and state the meaning of and distinguish between p-values and confidence intervals.
6. Interpret statistical significance for results from commonly used statistical tests.
7. Describe the similarities and differences between statistical tests, and state how to apply them appropriately.
8. Identify the use of survival analysis and different ways to perform and report it.

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of the chapter.

1. A randomized controlled trial assesses the effects of the treatment of heart failure on global functioning in three groups of adults after 6 months of treatment. Investigators wanted to assess global functioning with the New York Heart Association (NYHA) functional classification, an ordered scale from I to IV, and to compare the patient classification after 6 months of treatment. Which statistical test is most appropriate to assess differences in functional classification between the groups?
   A. Kruskal-Wallis test.
   B. Wilcoxon signed-rank test.
   C. Analysis of variance (ANOVA).
   D. Analysis of covariance (ANCOVA).

2. You are evaluating a randomized, double-blind, parallel-group controlled trial that compares four antihypertensive drugs for their effect on blood pressure. The authors conclude that hydrochlorothiazide is better than atenolol ($p<0.05$) and that enalapril is better than hydrochlorothiazide ($p<0.01$), but no difference is observed between any other drugs. The investigators used an unpaired (independent samples) t-test to test the hypothesis that each drug was equal to the other. Which statement is most appropriate?
   A. Investigators used the appropriate statistical test to analyze their data.
   B. Enalapril is the most effective of these drugs.
   C. ANOVA is a more appropriate test.
   D. A paired t-test is a more appropriate test.

3. In the results of a randomized, double-blind, controlled clinical trial, the difference in hospital readmission rates between the intervention group and the control group is 6% ($p=0.01$), and it is concluded that there is a statistically significant difference between the groups. Which statement is most consistent with this finding and conclusions?
   A. The chance of making a type I error is 5 in 100.
   B. The trial does not have enough power.
   C. There is a high likelihood of having made a type II error.
   D. The chance of making a type I error is 1 in 100.

4. You are reading a manuscript that evaluates the impact of obesity on enoxaparin pharmacokinetics. The authors used an unpaired t-test to compare the baseline values of body mass index (BMI) in normal subjects and obese subjects. You are evaluating the use of an unpaired t-test to compare the BMI between the two groups. Which choice best represents the most appropriate criteria to be met to use this parametric test?
   A. The sample sizes in the normal and obese subjects should be equal to allow the use of a t-test.
   B. A t-test is not appropriate because BMI data are ordinal.
   C. The variance of the BMI data has to be similar in each group.
   D. The pre-study power should be at least 90%.

5. You are evaluating the results and discussion of a journal club article to present to the pharmacy residents at your institution. The randomized, prospective, controlled trial evaluated the efficacy of a new controller drug for asthma. The primary end point was the morning forced expiratory volume in 1 second (FEV_1) in two groups of subjects (men and women). The difference in FEV_1 between the two groups was 15% (95% confidence interval [CI], 10%–21%). Which statement is most appropriate, given the results?
   A. Without the reporting of a p-value, it is not possible to conclude whether these results were statistically significant.
   B. There is a statistically significant difference between the men and women ($p<0.05$).
   C. There is a statistically significant difference between the men and women ($p<0.01$).
   D. There is no statistically significant difference between the men and women.

6. An early-phase clinical trial of 40 subjects evaluated a new drug known to increase high-density lipoprotein cholesterol (HDL) concentrations. The objective of the trial was to compare the new drug's ability to increase HDL with that of lifestyle modifications (active control group). At the beginning of the study, the mean baseline HDL was 37 mg/dL in the active control group and 38 mg/dL in the new drug group. At the end of the 3-month trial, the mean HDL for the control group was 44 mg/dL and for the new drug group, 49 mg/dL. The p-value for the comparison at 3 months was 0.08. Which statement provides the best interpretation of these results?
   A. An a priori α of less than 0.10 would have made the study more clinically useful.
   B. The new drug and active control appear to be equally efficacious in increasing HDL concentrations.
   C. The new drug is better than lifestyle modifications because it increases HDL concentrations to a greater extent.
   D. This study is potentially underpowered.

7. Researchers planned a study to evaluate the percentage of subjects who achieved less than a target blood pressure (less than 140/90 mm Hg) when initiating therapy with two different doses of amlodipine. In the study of 100 subjects, the amlodipine 5-mg group (n=50) and the amlodipine 10-mg group (n=50) were compared. The investigators used a blood pressure goal as their primary end point, defined as the percentage of subjects who successfully achieved the blood pressure goal at 3 months. Which is the most appropriate statistical test to answer such a question?
   A. Independent samples t-test.
   B. Chi-square or Fisher exact test.
   C. Wilcoxon signed-rank test.
   D. One-sample t-test.

8. An investigational drug is being compared with an existing drug for the treatment of anemia in patients with chronic kidney disease. The study is designed to detect a minimum 20% difference in response rates between the groups, if one exists, with an a priori α of 0.05 or less. The investigators are unclear whether the 20% difference between response rates is too large and think a smaller difference might be more clinically meaningful. In revising their study, they decide they want to be able to detect a minimum 10% difference in response. Which change to the study parameters is most appropriate?
   A. Increase the sample size.
   B. Select an α of 0.001 as a cutoff for statistical significance.
   C. Select an α of 0.10 as a cutoff for statistical significance.
   D. Decrease the sample size.

9. You are designing a new computer alert system to investigate the impact of several factors on the risk of corrected QT interval (QTc) prolongation. You want to develop a model to predict which patients are most likely to experience QTc prolongation after the administration of certain drugs or the presence of certain conditions. You plan to assess the presence or absence of several different variables. Which technique will be most useful in completing such an analysis?
   A. Correlation.
   B. Kaplan-Meier curve.
   C. Regression.
   D. Confidence intervals.

I. INTRODUCTION TO STATISTICS

A. Method for Collecting, Classifying, Summarizing, and Analyzing Data

B. Useful Tool for Quantifying Clinical and Laboratory Data in a Meaningful Way

C. Assists in Determining Whether and by How Much a Treatment or Procedure Affects a Group of Patients

D. Why Pharmacists Need to Know Statistics

E. As Statistics Pertains to Most of You
   1. Pharmacotherapy Specialty Examination content outline, Domain 2: Application of Evidence to Practice and Education (25%)
   2. Task statements:
      a. Retrieve information that addresses pharmacotherapy-related inquiries.
      b. Evaluate pharmacotherapy-related literature, databases, and health information.
      c. Disseminate pharmacotherapy-related information to educate health care professionals, patients, and caregivers.

F. Examples of Online Statistical and Study Design Tools
   1. www.graphpad.com/quickcalcs/
   2. http://statpages.org/

G. Several Papers Have Investigated the Various Types of Statistical Tests Used in the Biomedical Literature; the data from one of these papers are illustrated in the text that follows. Tables 1 and 2 are modified from Horton NJ, Switzer S. Statistical methods in the Journal. N Engl J Med 2005;353:1977-9 and Windish DM, Huot SJ, Green ML. Medicine resident's understanding of the biostatistics and results in the medical literature. JAMA 2007;298:1010-22, respectively.

Table 1. Statistical Content of Original Articles in *New England Journal of Medicine*, 2004–2005

Statistical Procedure	% of Articles Containing Methods	Statistical Procedure	% of Articles Containing Methods
No statistics or descriptive statistics	13	Adjustment and standardization	1
t-tests	26	Multiway tables	13
Contingency tables	53	Power analyses	39
Nonparametric tests	27	Cost-benefit analysis	< 1
Epidemiologic statistics	35	Sensitivity analysis	6
Pearson correlation	3	Repeated-measures analysis	12
Simple linear regression	6	Missing-data methods	8
Analysis of variance	16	Noninferiority trials	4
Transformation	10	Receiver operating characteristics	2
Nonparametric correlation	5	Resampling	2
Survival methods	61	Principal component and cluster analyses	2
Multiple regression	51	Other methods	4
Multiple comparisons	23		

Table 2. Statistical Content of Original Articles from Six Major Medical Journals from January to March 2005 (n=239 articles)[a]

Statistical Test	No. (%)	Statistical Test	No. (%)
Descriptive statistics (mean, median, frequency, SD, and IQR)	219 (91.6)	Others	
Simple statistics	120 (50.2)	Intention-to-treat analysis	42 (17.6)
Chi-square analysis	70 (29.3)	Incidence or prevalence	39 (16.3)
t-test	48 (20.1)	Relative risk or risk ratio	29 (12.2)
Kaplan-Meier analysis	48 (20.1)	Sensitivity analysis	21 (8.8)
Wilcoxon rank sum test	38 (15.9)	Sensitivity or specificity	15 (6.3)
Fisher exact test	33 (13.8)		
Analysis of variance	21 (8.8)		
Correlation	16 (6.7)		
Multivariate analysis	164 (68.6)		
Cox proportional hazards	64 (26.8)		
Multiple logistic regression	54 (22.6)		
Multiple linear regression	7 (2.9)		
Other regression analysis	38 (15.9)		
None	5 (2.1)		

[a]Articles published in *American Journal of Medicine*, *Annals of Internal Medicine*, *BMJ*, *Journal of the American Medical Association*, *Lancet*, and *New England Journal of Medicine*.

IQR = interquartile range; SD = standard deviation.

II. TYPES OF VARIABLES AND DATA

A. Definition: Random Variables—A variable with observed values that may be considered outcomes of an experiment and whose values cannot be anticipated with certainty before the experiment is conducted
B. Two Types of Random Variables
    1. Discrete variables (e.g., dichotomous, categorical)
    2. Continuous variables
C. Discrete Variables
    1. Can take only a limited number of values within a given range
    2. Nominal: Classified into groups in an unordered manner and with no indication of relative severity (e.g., male or female sex, mortality [dead or alive], disease presence [yes or no], race, marital status)
    3. Ordinal: Ranked in a specific order but with no consistent level of magnitude of difference between ranks (e.g., NYHA functional class describes the functional status of patients with heart failure, and subjects are classified in increasing order of symptoms: I, II, III, IV; Likert-type scales)
    4. Common error: Measure of central tendency—In most cases, means and standard deviations (SDs) should not be reported with ordinal data. What is a common incorrect use of means and SDs to show ordinal data?
D. Continuous Variables, Sometimes Called Counting Variables
    1. Continuous variables can take on any value within a given range.
    2. Interval: Data are ranked in a specific order with a consistent change in magnitude between units; the zero point is arbitrary (e.g., degrees Fahrenheit).
    3. Ratio: Like "interval" but with an absolute zero (e.g., degrees Kelvin, heart rate, blood pressure, time, distance)

III. TYPES OF STATISTICS

A. Descriptive Statistics: Used to summarize and describe data that are collected or generated in research studies. This is done both visually and numerically.
    1. Visual methods of describing data
        a. Frequency distribution
        b. Histogram
        c. Scatterplot
        d. Boxplot
    2. Numerical methods of describing data: Measures of central tendency
        a. Arithmetic mean (i.e., average)
            i. Sum of all values divided by the total number of values
            ii. Should generally be used only for continuous and normally distributed data
            iii. Very sensitive to outliers and tend toward the tail, which has the outliers
            iv. Most commonly used and most understood measure of central tendency
            v. Geometric mean
        b. Median
            i. Midpoint of the values when placed in order from highest to lowest. Half of the observations are above and half are below. When there is an even number of observations, it is the mean of the two middle values.
            ii. Also called 50th percentile
            iii. Can be used for ordinal or continuous data (especially good for skewed populations)
            iv. Insensitive to outliers

   c. Mode
      i. Most common value in a distribution
      ii. Can be used for nominal, ordinal, or continuous data
      iii. Sometimes, there may be more than one mode (e.g., bimodal, trimodal).
      iv. Does not help describe meaningful distributions with a large range of values, each of which occurs infrequently
3. Numerical methods of describing data: Measures of data spread or variability
   a. Standard deviation
      i. Measure of the variability about the mean; most common measure used to describe the spread of data
      ii. Square root of the variance (average squared difference of each observation from the mean); returns variance back to original units (non-squared)
      iii. Appropriately applied only to continuous data that are normally or near normally distributed or that can be transformed to be normally distributed
      iv. By the empirical rule for normal distributions, 68% of the sample values are found within ±1 SD, 95% are found within ±2 SD, and 99% are found within ±3 SD.
      v. The coefficient of variation relates the mean and the SD (SD/mean × 100%).
   b. Range
      i. Difference between the smallest and largest values in a data set does not give a tremendous amount of information by itself.
      ii. Easy to compute (simple subtraction)
      iii. Size of range is very sensitive to outliers.
      iv. Often reported as the actual values rather than the difference between the two extreme values
   c. Percentiles
      i. The point (value) in a distribution in which a value is larger than some percentage of the other values in the sample. Can be calculated by ranking all data in a data set
      ii. The 75th percentile lies at a point at which 75% of the other values are smaller.
      iii. Does not assume the population has a normal distribution (or any other distribution)
      iv. The interquartile range (IQR) is an example of the use of percentiles to describe the middle 50% values. The IQR encompasses the 25th–75th percentile.
4. Presenting data using only measures of central tendency can be misleading without some idea of data spread. Studies that report only medians or means without their accompanying measures of data spread should be closely scrutinized. What are the measures of spread that should be used with means and medians?
5. Example data set (Table 3)

Table 3. Twenty Baseline HDL Concentrations from an Experiment Evaluating the Impact of Green Tea on HDL

64	60	59	65	64	62	54
54	68	67	79	55	48	65
59	65	87	49	46	46	

   a. Calculate the mean, median, and mode of the data set given in Table 3.
   b. Calculate the range, and SD (on examination, you will most likely not have to do this by hand).
   c. Evaluate the visual presentation of the data.

B. Inferential Statistics
   1. Conclusions or generalizations made about a population (large group) from the study of a sample of that population
   2. Choosing and evaluating statistical methods depend, in part, on the type of data used.
   3. An educated statement about an unknown population is commonly called an inference in statistics.
   4. Statistical inference can be made by estimation or hypothesis testing.

IV. POPULATION DISTRIBUTIONS

A. Discrete Distributions
   1. Binomial distribution
   2. Poisson distribution

B. Normal (Gaussian) Distribution
   1. Most common model for population distributions
   2. Symmetric or bell-shaped frequency distribution
   3. Landmarks for continuous, normally distributed data
      a. μ: Population mean is equal to zero.
      b. σ: Population SD is equal to 1.
      c. $\bar{x}$ and s: These represent the sample mean and SD.
   4. When a random variable is measured in a large enough sample of any population, some values will occur more often than will others.
   5. A visual check of a distribution can help determine whether it is normally distributed (whether it appears symmetric and bell shaped). Need the data to perform these checks.
      a. Frequency distribution and histograms (visually look at the data; you should do this anyway)
      b. Median and mean will be about equal for normally distributed data (most practical and easiest to use).
      c. Formal test: Kolmogorov-Smirnov test and others
      d. More challenging to evaluate this when we do not have access to the data (when we are reading an article), because most articles do not present all data or both the mean and median
   6. The parameters mean and SD define a normally distributed population.
   7. Probability: The likelihood that any one event will occur given all the possible outcomes
   8. Estimation and sampling variability
      a. One method that can be used to make an inference about a population parameter
      b. Separate samples (even of the same size) from a single population will give slightly different estimates.
      c. The distribution of means from random samples approximates a normal distribution.
         i. The mean of this "distribution of means" is equal to the unknown population mean, μ.
         ii. The SD of the means is estimated by the standard error of the mean (SEM).
         iii. As in any normal distribution, 95% of the sample means lie within ±2 SEM of the population mean.
      d. The distribution of means from these random samples is about normal regardless of the underlying population distribution (central limit theorem). You will get slightly different mean and SD values each time you repeat this experiment.
      e. The SEM is estimated with a single sample by dividing the SD by the square root of the sample size (n). The SEM quantifies uncertainty in the estimate of the mean, not variability in the sample. Important for hypothesis testing and 95% CI estimation

f. Why is all this information about the difference between the SEM and SD worth knowing?
   i. Calculation of CIs. (95% CI is approximately the mean ± 2 times the SEM.)
   ii. Hypothesis testing
   iii. Deception (e.g., makes results look less "variable," especially when used in graphic format)

9. Recall the previous example about HDL and green tea. From the calculated values in section III, do these data appear to be normally distributed?

V. CONFIDENCE INTERVALS

A. Commonly Reported as a Way to Estimate a Population Parameter
   1. In the medical literature, 95% CIs are the most commonly reported CIs. In repeated samples, 95% of all CIs include true population value (i.e., the likelihood or confidence [or probability] that the population value is contained within the interval). In some cases, 90% or 99% CIs are reported. Why are 95% CIs most often reported?
   2. Example
      a. Assume a baseline birth weight in a group (n=51) with a mean ± SD of 1.18 ± 0.4 kg.
      b. 95% CI is about equal to the mean ± 1.96 × SEM (or 2 × SEM). In reality, it depends on the distribution being used and is a bit more complicated.
      c. What is the 95% CI? The 95% CI is calculated to be (1.07, 1.29), meaning there is 95% certainty that the true mean of the entire population studied will be 1.07–1.29 kg.
      d. What is the 90% CI? The 90% CI is calculated to be (1.09, 1.27). The 95% CI will always be wider than the 90% CI for any given sample. Therefore, the wider the CI, the more likely it is to encompass the true population mean.
   3. The differences between the SD, SEM, and CIs should be noted when interpreting the literature because they are often used interchangeably. Although it is common for CIs to be confused with SDs, the information each provides is quite different and has to be assessed correctly.
   4. Recall the previous example about HDL and green tea. What is the 95% CI of the data set, and what does that mean?

B. CIs Can Also Be Used for Any Sample Estimate. Estimates derived from categorical data such as risk, risk differences, and risk ratios are often presented with the CI and will be discussed in the text that follows.

C. CIs Instead of Hypothesis Testing
   1. Hypothesis testing and calculation of p-values tell us (ideally) whether there is or is not a statistically significant difference between groups, but they do not tell us anything about the magnitude of the difference.
   2. CIs help us determine the importance of a finding or findings, which we can apply to a situation.
   3. CIs give us an idea of the magnitude of the difference between groups and the statistical significance.
   4. CIs are a range of data, together with a point estimate of the difference.
   5. Wide CIs
      a. Many results are possible, either larger or smaller than the point estimate provided by the study.
      b. All values contained in the CI are statistically plausible.
   6. If the estimate is the difference between two continuous variables: A CI that includes zero (no difference between two variables) can be interpreted as not statistically significant (a p-value of 0.05 or greater). There is no need to show both the 95% CI and the p-value.

7. The interpretation of CIs for odds ratios and relative risks is somewhat different. In that case, a value of 1 indicates no difference in risk, and if the CI includes 1, there is no statistical difference. (See the discussion of case-control/cohort studies in other sections for how to interpret CIs for odds ratios and relative risks.)

VI. HYPOTHESIS TESTING

A. Null and Alternative Hypotheses (see Table 4 for other types of examples)
   1. Null hypothesis (H_0): Example: No difference between groups being compared (treatment A equals treatment B)
   2. Alternative hypothesis (H_A): Example: Opposite of null hypothesis; states that there is a difference (treatment A does not equal treatment B)
   3. The structure or the manner in which the hypothesis is written dictates which statistical test is used. Two-sample t-test: H_0: Mean 1 = Mean 2
   4. Used to assist in determining whether any observed differences between groups can be explained by chance
   5. Tests for statistical significance (hypothesis testing) determine whether the data are consistent with H_0 (no difference).
   6. The results of the hypothesis testing will indicate whether enough evidence exists for H_0 to be rejected.
      a. If H_0 is rejected: Statistically significant difference between groups (unlikely attributable to chance)
      b. If H_0 is not rejected: No statistically significant difference between groups (any apparent differences may be attributable to chance). Note that we are not concluding that the treatments are equal.
   7. Types of hypothesis testing. These are situations in which two groups are being compared. There are numerous other examples of situations these procedures could be applied to (Table 4).

Table 4. Types of Hypothesis Testing

	Question	Hypothesis	Method
Nondirectional			
Difference	Are the means different?	H_0: $Mean_1 = Mean_2$ H_A: $Mean_1 \neq Mean_2$ or H_0: $Mean_1 - Mean_2 = 0$ H_A: $Mean_1 - Mean_2 \neq 0$	Traditional 2-sided t-test Confidence intervals
Equivalence	Are the means practically equivalent?	H_0: $Mean_1 - Mean_2 \geq \Delta$ H_A: $Mean_1 - Mean_2 < \Delta$	Two 1-sided t-test (TOST) procedure Confidence intervals
Directional			
Superiority	Is mean 1 > mean 2? (or some other similarly worded question)	H_0: $Mean_1 \leq Mean_2$ H_A: $Mean_1 > Mean_2$ or H_0: $Mean_1 - Mean_2 \leq 0$ H_A: $Mean_1 - Mean_2 > 0$	Traditional 1-sided t-test Confidence intervals
Noninferiority	Is mean 1 no more than a certain amount lower than mean 2?	H_0: $Mean_1 - Mean_2 \geq \Delta$ H_A: $Mean_1 - Mean_2 < \Delta$	Confidence intervals

Δ = equivalence or noninferiority margin; H_0 = null hypothesis; H_A = alternative hypothesis.

B. To Determine What Is Sufficient Evidence to Reject H_0: Set the a priori significance level (α) and generate the decision rule.
   1. Developed after the research question has been stated in hypothesis form
   2. Used to determine the level of acceptable error caused by a false positive (also known as level of significance)
      a. Convention: A priori α is usually 0.05.
      b. Critical value is calculated, capturing how extreme the sample data must be to reject H_0.

C. Perform the Experiment and Estimate the Test Statistic.
   1. A test statistic is calculated from the observed data in the study, which is compared with the critical value.
   2. Depending on this test statistic's value, H_0 is not rejected (often called fail to reject) or rejected.
   3. In general, the test statistic and critical value are not presented in the literature; instead, p-values are generally reported and compared with a priori α values to assess statistical significance. p-value: Probability of obtaining a test statistic and critical value as extreme as or more extreme than the one actually obtained
   4. Because computers are used in these tests, this step is often transparent; the p-value estimated in the statistical test is compared with the a priori α (usually 0.05), and the decision is made.

VII. STATISTICAL TESTS AND CHOOSING A STATISTICAL TEST

A. Which Tests Do You Need to Know?

B. Choosing the Appropriate Statistical Test Depends on the Following:
   1. Type of data (nominal, ordinal, or continuous)
   2. Distribution of data (e.g., normal)
   3. Number of groups
   4. Study design (e.g., parallel, crossover)
   5. Presence of confounding variables
   6. One-tailed versus two-tailed
   7. Parametric versus nonparametric tests
      a. Parametric tests assume the following:
         i. Data being investigated have an underlying distribution that is normal or close to normal or, more correctly, randomly drawn from a parent population with a normal distribution. Remember how to estimate this (mean ~ median)?
         ii. Data measured are continuous data, measured on either an interval or a ratio scale.
         iii. Parametric tests assume that the data being investigated have variances that are homogeneous between the groups investigated. This is often called homoscedasticity.
      b. Nonparametric tests are used when data are not normally distributed or do not meet other criteria for parametric tests (e.g., discrete data).

C. Parametric Tests
   1. Student t-test: Several different types
      a. One-sample test: Compares the mean of the study sample with the population mean

Group 1	Known population mean

      b. Two-sample, independent samples, or unpaired test: Compares the means of two independent samples. This is an independent samples test.

Group 1	Group 2

         i. Equal variance test
            (a) Rule for variances: If the ratio of larger variance to smaller variance is greater than 2, we generally conclude the variances are different.
            (b) Formal test for differences in variances: F test
            (c) Adjustments can be made for cases of unequal variance.
         ii. Unequal variance
      c. Paired test: Compares the mean difference of paired or matched samples. This is a related samples test.

Group 1	
Measurement 1	Measurement 2

      d. Common error: Use of multiple t-tests with more than two groups
   2. Analysis of variance (ANOVA): A more generalized version of the t-test that can apply to more than two groups
      a. One-way ANOVA: Compares the means of three or more groups in a study; also known as single-factor ANOVA. This is an independent samples test.

Group 1	Group 2	Group 3

      b. Two-way ANOVA: Additional factor (e.g., age) added

Young groups	Group 1	Group 2	Group 3
Old groups	Group 1	Group 2	Group 3

      c. Repeated-measures ANOVA: This is a related samples test.

	Related Measurements		
Group 1	Measurement 1	Measurement 2	Measurement 3

      d. Several more complex factorial ANOVAs can be used.
      e. Many comparison procedures are used to determine which groups actually differ from each other. Post hoc tests: Tukey HSD (Honestly Significant Difference), Bonferroni, Scheffé, Newman-Keuls
   3. Analysis of covariance (ANCOVA): Provides a method to explain the influence of a categorical variable (independent variable) on a continuous variable (dependent variable) while statistically controlling for other variables (confounding)

D. Nonparametric Tests
   1. These tests may also be used for continuous data that do not meet the assumptions of the t-test or ANOVA.
   2. Tests for independent samples
      a. Wilcoxon rank sum test, Mann-Whitney *U* test, or Wilcoxon Mann-Whitney test: Compare two independent samples (related to a t-test)
      b. Kruskal-Wallis one-way ANOVA by ranks
         i. Compares three or more independent groups (related to one-way ANOVA)
         ii. Post hoc testing
   3. Tests for related or paired samples
      a. Sign test and Wilcoxon signed-rank test: Compares two matched or paired samples (related to a paired t-test)
      b. Friedman ANOVA by ranks: Compares three or more matched or paired groups

E. Nominal Data
   1. Chi-square (χ^2) test: Compares expected and observed proportions between two or more groups
      a. Test of independence
      b. Test of goodness of fit
   2. Fisher exact test: Specialized version of the chi-square test for small groups (cells) containing less than five predicted observations
   3. McNemar: Paired samples
   4. Mantel-Haenszel: Controls for the influence of confounders

F. Correlation and Regression (see section IX)

G. Choosing the Most Appropriate Statistical Test: Example 1
   1. A trial was conducted to determine the efficacy and safety of alirocumab in reducing lipids and cardiovascular events. Alirocumab plus statins was compared with placebo plus statins regarding their effect on low-density lipoprotein cholesterol (LDL) concentrations. The trial was designed such that the subjects' baseline characteristics were as comparable as possible with each other. *The intended primary end point for this trial was the difference in LDL between the two treatments at week 24.* The full trial is published: N Engl J Med 2015;372:1489-99. Note that only partial results are presented. The results of the trial are reported as follows:

Table 5. Baseline Characteristics and Alirocumab and Placebo Effect on LDL[a]

	Alirocumab plus Statins (n=1553)	**Placebo plus Statins (n=788)**
Men/women	(63.3%) 983/570	(60.2%) 474/314
Smokers	(20.9%) 325/1228	(20.2%) 159/629
Baseline LDL, mg/dL	122.8 ± 42.7	122.0 ± 41.6
Final LDL, mg/dL	48.3 ± 35.2	118.9 ± 33.5

[a]Data are presented as mean ± SD.

2. Which is the appropriate statistical test to determine baseline differences in the following:
   a. Sex distribution?
   b. LDL?
   c. Percentage of smokers and nonsmokers?
3. Which is the appropriate statistical test to determine the following:
   a. The effect of alirocumab plus statins on LDL?
   b. The primary end point?

VIII. DECISION ERRORS

Table 6. Summary of Decision Errors

	Underlying Truth or Reality	
Test Result	*H_0 is true* (no difference)	*H_0 is false* (difference)
Accept H_0 (no difference)	No error (correct decision)	Type II error (β error)
Reject H_0 (difference)	Type I error (α error)	No error (correct decision)

H_0 = null hypothesis.

A. Type I Error: The probability of making this error is defined as the significance level α.
   1. Convention is to set the α to 0.05, effectively meaning that, 1 in 20 times, a type I error will occur when the H_0 is rejected. Thus, 5.0% of the time, a researcher will conclude that there is a statistically significant difference when one does not actually exist.
   2. The calculated chance that a type I error has occurred is called the p-value.
   3. The p-value tells us the likelihood of obtaining a given (or a more extreme) test result if the H_0 is true. When the α level is set a priori, H_0 is rejected when p is less than α. In other words, the p-value tells us the probability of being wrong when we conclude that a true difference exists (false positive).
   4. A lower p-value does not mean the result is more important or more meaningful but only that it is statistically significant and not likely to be attributable to chance.

B. Type II Error: The probability of making this error is called beta.
   1. Concluding that no difference exists when one truly does (not rejecting H_0 when it should be rejected)
   2. It has become a convention to set β at 0.20–0.10.

C. Power (1 − β)
   1. The probability of making a correct decision when H_0 is false; the ability to detect differences between groups if one actually exists
   2. Dependent on the following factors:
      a. Predetermined α
      b. Sample size
      c. The size of the difference between the outcomes you want to detect. Often not known before conducting the experiment, so to estimate the power of your test, you will have to specify how large a change is worth detecting
      d. The variability of the outcomes that are being measured
      e. Items c and d are generally determined from previous data or the literature.

3. Power is decreased by the following (in addition to the earlier criteria):
   a. Poor study design
   b. Incorrect statistical tests (use of nonparametric tests when parametric tests are appropriate)
4. Statistical power analysis and sample size calculation
   a. Related to the previous discussion of power and sample size
   b. Sample size estimates should be performed in all studies a priori.
   c. Necessary components for estimating appropriate sample size
      i. Acceptable type II error rate (usually 0.10–0.20)
      ii. Observed difference in predicted study outcomes that is clinically significant
      iii. The expected variability in item ii
      iv. Acceptable type I error rate (usually 0.05)
      v. Statistical test that will be used for primary end point
5. Statistical significance versus clinical significance
   a. As stated earlier, the size of the p-value is not necessarily related to the clinical importance of the result. Smaller values mean only that chance is less likely to explain observed differences.
   b. Statistically significant does not necessarily mean clinically significant.
   c. Lack of statistical significance does not mean that results are not clinically important.
   d. When considering nonsignificant findings, consider sample size, estimated power, and observed variability.

IX. CORRELATION AND REGRESSION

A. Introduction: Correlation vs. Regression
   1. Correlation examines the strength of the association between two variables. It does not necessarily assume that one variable is useful in predicting the other.
   2. Regression examines the ability of one or more variables to predict another variable.

B. Pearson Correlation
   1. The strength of the relationship between two variables that are normally distributed, ratio or interval scaled, and linearly related is measured with a correlation coefficient.
   2. Often called the degree of association between the two variables
   3. Does not necessarily imply that one variable is dependent on the other (regression analysis will do that)
   4. Pearson correlation (r) ranges from −1 to +1 and can take any value in between:

−1	0	+1
Perfect negative linear relationship	No linear relationship	Perfect positive linear relationship

   5. Hypothesis testing is performed to determine whether the correlation coefficient is different from zero. This test is highly influenced by sample size.

C. Pearls About Correlation
   1. The closer the magnitude of r to 1 (either + or −), the more highly correlated the two variables. The weaker the relationship between the two variables, the closer r is to 0.
   2. There is no agreed-on or consistent interpretation of the value of the correlation coefficient. It is dependent on the environment of the investigation (laboratory vs. clinical experiment).

3. Pay more attention to the magnitude of the correlation than to the p-value because it is influenced by sample size.
4. Crucial to the proper use of correlation analysis is the interpretation of the graphic representation of the two variables. Before using correlation analysis, it is essential to generate a scatterplot of the two variables to visually examine the relationship.

D. Spearman Rank Correlation: Nonparametric test that quantifies the strength of an association between two variables but does not assume a normal distribution of continuous data. Can be used for ordinal data or nonnormally distributed continuous data

E. Regression
   1. A statistical technique related to correlation. There are many different types. For simple linear regression, one continuous outcome (dependent) variable and one continuous independent (causative) variable
   2. Two main purposes of regression: Development of prediction model and accuracy of prediction
   3. Prediction model: Making predictions of the dependent variable from the independent variable; $Y = mx + b$ (dependent variable = slope × independent variable + intercept)
   4. Accuracy of prediction: How well the independent variable predicts the dependent variable. Regression analysis determines the extent of variability in the dependent variable that can be explained by the independent variable.
      a. Coefficient of determination (r^2) measured describing this relationship. Values of r^2 can range from 0 to 1.
      b. An r^2 of 0.80 could be interpreted as saying that 80% of the variation in *Y* is explained by the variation in *X*.
      c. This does not provide a mechanistic understanding of the relationship between *X* and *Y* but rather a description of how clearly such a model (linear or otherwise) describes the relationship between the two variables.
      d. Like the interpretation of r, the interpretation of r^2 is dependent on the scientific arena (e.g., clinical research, basic research, social science research) to which it is applied.
   5. For simple linear regression, two statistical tests can be used.
      a. To test the hypothesis that the *y*-intercept differs from zero
      b. To test the hypothesis that the slope of the line is different from zero
   6. Regression is useful in constructing predictive models. The literature is full of examples of predictions. The process involves developing a formula for a regression line that best fits the observed data.
   7. Like correlation, there are many different types of regression analysis.
      a. Multiple linear regression: One continuous independent variable and two or more continuous dependent variables
      b. Simple logistic regression: One categorical response (dependent) variable and one continuous or categorical explanatory (independent) variable
      c. Multiple logistic regression: One categorical response (dependent) variable and two or more continuous or categorical explanatory (independent) variables
      d. Nonlinear regression: Variables are not linearly related (or cannot be transformed into a linear relationship). This is where our pharmacokinetic equations come from.
      e. Polynomial regression: Any number of response and continuous variables with a curvilinear relationship (e.g., cubed, squared)

8. Example of regression
    a. The following data are taken from a study evaluating enoxaparin use. The authors were interested in predicting patient response (measured as anti-factor Xa concentrations) from the enoxaparin dose in the 75 subjects who were studied.

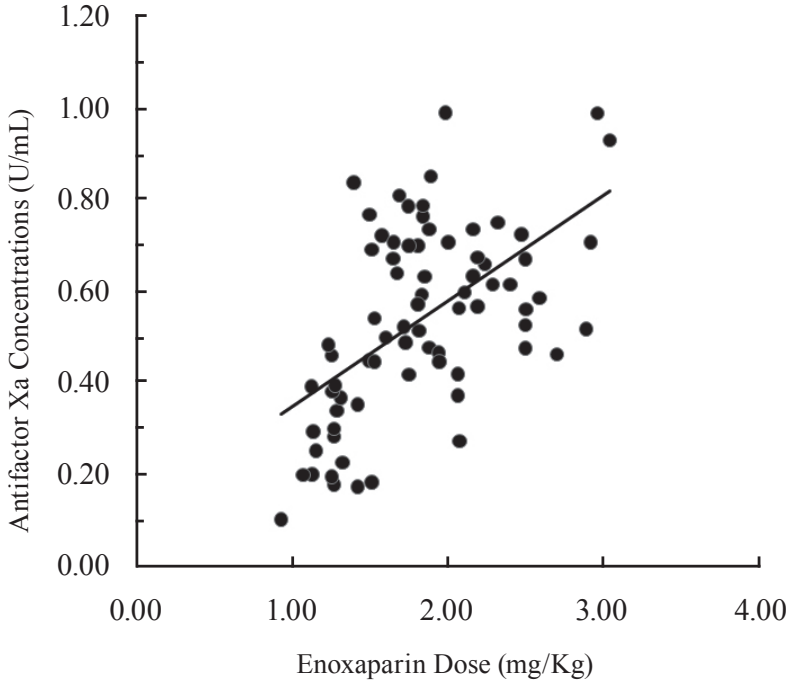

Figure 1. Relationship between antifactor Xa concentrations and enoxaparin dose.

    b. The authors performed regression analysis and reported the following: Slope: 0.227, *y*-intercept: 0.097, $p<0.05$, $r^2 = 0.31$.
    c. Answer the following questions:
        i. What are the assumptions necessary to use regression analysis?
        ii. Provide an interpretation of the coefficient of determination.
        iii. Predict anti-factor Xa concentrations at enoxaparin doses of 2 and 3.75 mg/kg.
        iv. What does the $p<0.05$ value indicate?

X. SURVIVAL ANALYSIS

A. Studies the Time Between Entry in a Study and Some Event (e.g., death, myocardial infarction)
    1. Censoring makes survival methods unique; considers that some subjects leave the study for reasons other than the event (e.g., lost to follow-up, end of study period)
    2. Considers that all subjects do not enter the study at the same time
    3. Standard methods of statistical analysis such as t-tests and linear or logistic regression may not be appropriately applied to survival data because of censoring.

B. Estimating the Survival Function
   1. Kaplan-Meier method
      a. Uses survival times (or censored survival times) to estimate the proportion of people who would survive a given length of time under the same circumstances
      b. Allows the production of a table (life table) and a graph (survival curve)
      c. We can visually evaluate the curves, but we need a test to evaluate them formally.
   2. Log-rank test: Compare the survival distributions between two or more groups.
      a. This test precludes an analysis of the effects of several variables or the magnitude of difference between groups or the CI (see the text that follows for the Cox proportional hazards model).
      b. H_0: No difference in survival between the two populations
      c. Log-rank test uses several assumptions.
         i. Random sampling and subjects chosen independently
         ii. Consistent criteria for entry or end point
         iii. Baseline survival rate does not change as time progresses.
         iv. Censored subjects have the same average survival time as uncensored subjects.
   3. Cox proportional hazards model
      a. Most popular method to evaluate the impact of covariates; reported graphically like Kaplan-Meier
      b. Investigates several variables at a time
      c. Actual method of construction and calculation is complex.
      d. Compares survival in two or more groups after adjusting for other variables
      e. Allows calculation of a hazard ratio (and CI)

XI. SELECTED REPRESENTATIVE STATISTICAL TESTS

Table 7. Representative Statistical Tests[a]

Type of Variable	2 Groups (independent)	2 Groups (related)	> 2 Groups (independent)	> 2 Groups (related)
Nominal	χ^2 or Fisher exact test	McNemar test	χ^2	Cochran *Q*
Ordinal	Wilcoxon rank sum Mann-Whitney *U* test Wilcoxon–Mann-Whitney	Wilcoxon signed-rank Sign test	Kruskal-Wallis (MCP)	Friedman ANOVA
Continuous No factors	Equal variance t-test Unequal variance t-test	Paired t-test	One-way ANOVA (MCP)	Repeated-measures ANOVA
1 factor	ANCOVA	Two-way repeated-measures ANOVA	Two-way ANOVA (MCP)	Two-way repeated-measures ANOVA

[a]For expanded table, see: DiCenzo R, ed. Clinical Pharmacist's Guide to Biostatistics and Literature Evaluation. Lenexa, KS: ACCP, 2015.

ANCOVA = analysis of covariance; ANOVA = analysis of variance; MCP = multiple-comparisons procedure.

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ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A

The NYHA functional class is an ordinal scale from I (no symptoms) to IV (severe symptoms). Neither ANOVA nor ANCOVA is appropriate for ordinal or noncontinuous data (Answers C and D are incorrect). The Wilcoxon signed-rank test is an appropriate nonparametric test to use for paired ordinal data, such as the change in NYHA functional class over time on the same person (Answer B is incorrect). The Kruskal-Wallis test is the nonparametric analog of a one-way ANOVA and is appropriate for this analysis (Answer A is correct).

2. Answer: C

You cannot determine which finding is more important (in this case, the best drug) on the basis of the p-value (i.e., a lower p-value does not mean more important) (Answer B is incorrect). All statistically significant results are interpreted as significant without respect to the size of the p-value. This trial had four independent samples, and use of the unpaired (independent samples) t-test is not appropriate because it requires several unnecessary tests and increases the chances of making a type I error (Answer A is incorrect). In this setting, ANOVA is the correct test (Answer C is correct), followed by a multiple-comparisons procedure to determine where the actual differences between groups lie. A paired t-test is inappropriate because this is a parallel-group trial (Answer D is incorrect). Use of ANOVA in this case assumes a normal distribution and equal variance in each of the four groups.

3. Answer: D

The typical a priori α error (type I) rate is 5% (i.e., when the study was designed, the error rate was designed to be 5% or less). The actual type I error rate is reported in the question as 0.01 (1%) (Answer A is incorrect). Answers B and C are related; the study did have enough power because a statistically significant difference was observed. Similarly, a type II error was not made because this error has to do with not finding a difference when one truly exists. In this question, the type I error rate is 1%, the value of the p-value (Answer D is correct).

4. Answer: C

Sample sizes need not be equal to use a t-test (Answer A is incorrect). Body mass index data are not ordinal but continuous; thus, a t-test is appropriate (Answer B is incorrect). The assumption of equal variances is required to use any parametric test (Answer C is correct). A specific value for power is not required to use a test (Answer D is incorrect).

5. Answer: B

The reporting of the mean difference and CI is thought by many to be a superior means of presenting the results from a clinical trial because it describes both precision and statistical significance, as compared with a p-value, which distills everything into one value, making Answer A incorrect. The presentation of the data in this manner clearly shows all the necessary information for making the appropriate conclusion. To assess statistical significance by use of CIs, the 95% CI (corresponding to the 5% type I error rate used in most studies) may not contain zero (signifying no difference between men and women) for the mean difference, making Answer D incorrect. Answer B is correct because the p-value of less than 0.05 corresponds to the 95% CI in that item. To evaluate Answer C, we would need to know the 99% CI.

6. Answer: D

Answer A is incorrect because it uses unconventional approaches to determine statistical significance. Although this can be done, it is unlikely to be accepted by other readers and investigators. This study observed a nonsignificant increase in HDL concentration between the two groups. With a small sample size, such as the one used in this study, there is always concern about adequate power to observe a difference between the two treatments. A difference may exist between these two drugs, but the number of subjects studied may be too small to detect it statistically. Answer D is correct because, with the lack of information provided in this narrative, it is not possible to estimate power; thus, more information is needed. Answer B may be correct, but without first addressing the question of adequate power, it would be an inappropriate conclusion to draw. Answer C is incorrect because even though the new drug increased HDL concentration more than the other treatment, it is inappropriate to conclude that it is better because, statistically, it is not.

7. Answer: B

The primary end point in this study, the percentage of subjects at or below the target blood pressure, is nominal data. Subjects at target blood pressure (less than 140/90 mm Hg) are defined as having reached the target. This type of data requires either a chi-square test or a Fisher exact test (depending on the sample size or, more accurately, the number of counts in the individual contingency table cells) (Answer B is correct). An independent samples t-test is not appropriate because actual blood pressure values are not being compared (at least not in this question or this end point) (Answer A is incorrect). If we were comparing the actual blood pressure between the two groups, the test might be appropriate if parametric assumptions were met. The Wilcoxon signed-rank test is the appropriate nonparametric test for comparing paired samples (usually in a crossover trial) (Answer C is incorrect). Finally, a one-sample t-test is used to compare the mean of a single group with the mean of a reference group. This is also incorrect in this situation because two groups are being compared (Answer D is incorrect).

8. Answer: A

Detecting the smaller difference between the treatments requires more power. Power can be increased in several different ways. Answer A is correct because the most common approach is to increase the sample size, which is expensive for the researchers. Answer D is incorrect because smaller sample sizes diminish a study's ability to detect differences between groups. Power can also be increased by increasing α, but doing so increases the chances of a type I error. Answer B decreases α, thus making it more difficult to detect differences between groups. Answer C certainly makes it easier to detect a difference between the two groups, but it uses an unconventional α value and is thus not the most appropriate technique.

9. Answer: C

Regression analysis is the most effective way to develop models to predict outcomes or variables (Answer C is correct). There are many different types of regression, but all share the ability to evaluate the impact of multiple variables simultaneously on an outcome variable. Correlation analysis is used to assess the association between two (or more) variables, not to make predictions (Answer A is incorrect). Kaplan-Meier curves are used to graphically depict survival curves or time to an event (Answer B is incorrect). Confidence intervals are not used to make predictions (Answer D is incorrect).

Study Designs: Fundamentals, Interpretation, and Research Topics

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Learning Objectives

1. Define, compare, and contrast the concepts of internal and external validity, bias, and confounding in clinical study design, and identify potential sources in clinical trials.
2. Outline the hierarchy of evidence generated by various study designs, and compare and contrast the advantages and disadvantages of various study designs.
3. Select from various biostatistical measures to appropriately compare groups or their assessments from various study designs, and use their findings/output to interpret results.
4. Define and evaluate odds, odds ratio, risk/incidence rate, risk ratio/relative risks (RRs), and other risk estimates.
5. Compute and evaluate number needed to treat and number needed to harm. Define point and period prevalence, incidence rate, prevalence rate, absolute risk difference, and RR difference.
6. Define research and differentiate it from quality improvement activities.
7. Describe the various steps of the professional writing and peer-review processes.

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of the chapter.

Questions 1 and 2 pertain to the following case.

A recently released statin is associated with less myopathy than other currently available statins. After 2 years of use, a retrospective case-control study was undertaken by the manufacturer after 20 different reports of severe myopathy were sent to the U.S. Food and Drug Administration's (FDA's) MedWatch program. Risk factors for statin-induced myopathy were not assessed; however, both the cases and the controls of this study had identical diagnostic evaluations and were stratified according to the duration of statin use before the onset of myopathy.

1. Which type of bias is this study design most susceptible to?
   A. Confounding by indication.
   B. Recall bias.
   C. Diagnostic bias.
   D. Misclassification.

2. Which factor will be most affected by the type of bias likely to occur in this study?
   A. External validity.
   B. Internal validity.
   C. Assessment of exposure.
   D. Number of patients needed for the study.

3. When describing the results of a randomized controlled clinical trial, the investigators report using an intention-to-treat analysis to analyze their data. The results of their investigation comparing two diuretics for heart failure show no difference in the number of hospitalizations for decompensated heart failure between the treatment groups. Given their method of data analysis, which statement is most appropriate?
   A. May be susceptible to issues regarding recall bias.
   B. Provides a good measure of effectiveness under typical clinical conditions.
   C. Cannot provide an estimate of the method's effectiveness.
   D. May overestimate the actual treatment effect.

4. A prospective randomized study compared once-daily enoxaparin with twice-daily enoxaparin when treating patients with venous thromboembolism (VTE). One of the study end points was the recurrence of VTE. The following table summarizes recurrence rates in all patients.

	Once Daily	**Twice Daily**
All patients, n (%)	13/298 (4.4)	9/312 (2.9)

   The 95% confidence interval (CI) for the difference in recurrence rates between the two groups was −1.5% to 4.5%. Which conclusion is most appropriate?
   A. Twice-daily enoxaparin is superior to once daily
   B. Superiority of twice-daily enoxaparin could not be established over once daily.

C. Once-daily enoxaparin is not inferior to twice daily.

D. No conclusion can be drawn because p-values are unavailable.

5. According to the data in the previous question and the result obtained, which best represents the number of patients who would need to be treated with twice-daily enoxaparin to prevent the recurrence of one VTE episode?

A. Number needed to treat (NNT) would be 2.

B. NNT would be 67.

C. NNT would be 152.

D. NNT should not be calculated because the result was nonsignificant.

Questions 6 and 7 pertain to the following case.

A multicenter, double-blind, placebo-controlled trial randomly assigned 4837 patients to treatment with margarine supplemented with the omega-3 fatty acid α-linolenic acid (ALA) (margarine with ALA) or a placebo margarine. The primary combined end point was the rate of cardiovascular events, defined as fatal and nonfatal cardiovascular events and percutaneous coronary interventions. Data were analyzed according to intention-to-treat analysis with the use of a Cox proportional hazards model. The hazard ratio (HR) and 95% CI for the margarine with ALA group were 0.91 and 0.78–1.05, respectively. In the prespecified subgroup of women, margarine with ALA was associated with an HR of 0.73 (95% CI, 0.51–1.03).

6. Which statement is most appropriate?

A. Margarine with ALA statistically significantly reduced the risk of cardiovascular events ($p<0.05$).

B. Margarine with ALA statistically significantly reduced the risk of cardiovascular events ($p<0.01$).

C. Margarine with ALA did not significantly reduce the risk of cardiovascular events ($p>0.05$).

D. Without a p-value, it is not possible to determine whether margarine with ALA affected cardiovascular events.

7. When the study was being designed, which choice describes the outcome for which the study was most likely to have been powered?

A. Differences in the rate of the composite outcome, cardiovascular events.

B. Differences in the rate of percutaneous coronary interventions.

C. Differences in the rate of the composite outcomes in women.

D. Differences in the rate of the composite outcomes in men.

8. In a meta-analysis of studies examining the effects of several antihypertensive drugs, the odds ratio (OR) for treatment with low-dose diuretics compared with calcium channel blockers for cardiovascular disease events was 0.84 (95% CI, 0.75–0.95). Which statement is the most appropriate interpretation of these findings?

A. Treatment of hypertension with low-dose diuretics was more effective in preventing cardiovascular disease events than treatment with calcium channel blockers.

B. Treatment of hypertension with calcium channel blockers was more effective in preventing cardiovascular disease events than treatment with low doses of diuretics.

C. The difference observed between treatment with calcium channel blockers and low doses of diuretics is not statistically significant.

D. The odds of developing cardiovascular events when treating hypertension with low doses of diuretics are lower than when using calcium channel blockers.

9. According the Code of Federal Regulations, which statement best describes what is required of IRB membership?

A. At least one layperson must serve on the IRB.

B. The size of IRB membership changes depending on the institution size.

C. At least 10 members serve on the IRB.

D. There must be one physician on the IRB.

10. As a resident who recently completed a research project, you are writing the introduction section of the paper. Which piece of information should best be included in this section?
    A. Information related to process for the selection of participants.
    B. Summary of prior studies.
    C. The average age of the study subjects
    D. Acknowledgments to clerical staff.

I. INTRODUCTION: WHY DO PHARMACISTS NEED TO KNOW ABOUT STUDY DESIGN AND INTERPRETATION?

A. Pharmacotherapy Specialty Examination content outline, Domain 2: Application of Evidence to Practice and Education (25%)

B. Task Statements:
   1. Retrieve information that addresses pharmacotherapy-related inquiries.
   2. Evaluate pharmacotherapy-related literature, databases, and health information.
   3. Disseminate pharmacotherapy-related information to educate health care professionals, patients, and caregivers.

II. VARIOUS CONCEPTS IN STUDY DESIGN

A. Research Design Classification
   1. Study purpose: Descriptive versus analytical
   2. Time orientation: Prospective versus retrospective design
      a. Prospective: Begin in the present and progress forward, collecting data from subjects whose outcomes lie in the future.
      b. Retrospective: Begin and end in the present; however, this design involves a major backward look to collect information about events that occurred in the past.
   3. Investigator orientation:
      a. Experimental trials
      b. Quasi-experimental trials
      c. Observational trials

B. Relative Strength of Evidence: Hierarchy of Study Designs

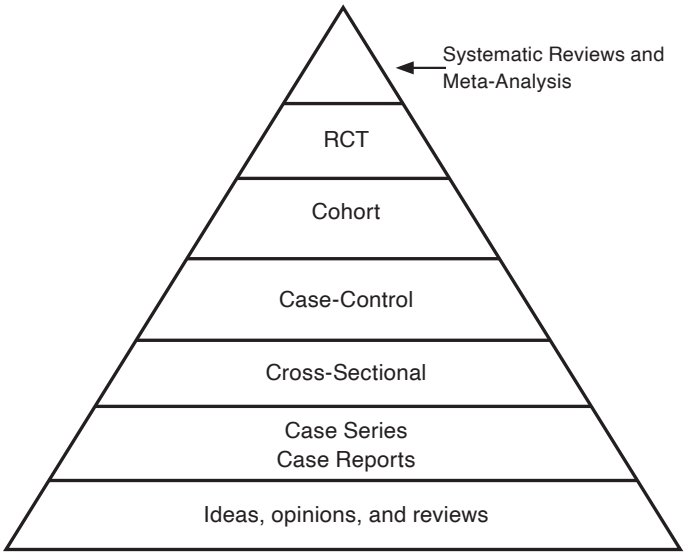

Figure 1. Hierarchy of clinical study design.
RCT = randomized controlled clinical trial.

C. Validity in Study Design
   1. Internal validity
      a. Validity within the confines of the study methods
      b. Does the study design adequately and appropriately test/measure what it purports?
      c. Does the study adequately and appropriately address bias, confounding, and measurement of end points?
   2. External validity
      a. Validity related to generalizing the study results outside the study setting
      b. Can the results be applied to other groups, patients, or systems?
      c. Addresses issues of generalizability and representativeness

D. Bias in Study Design
   1. Definition: Systematic, nonrandom variation in study methodology and conductance, ultimately introducing error in outcome interpretation. Bias can occur in all aspects of the study design.
   2. Examples of bias
      a. Selection bias: An error in the selection of or sampling of individuals for a clinical study. Classic example: subjects chosen for the case and control groups differ in one or more characteristics that alter the outcome of a study
      b. Observational or information bias: An error in the recording of individual factors of a study, such as inaccurate recording of a patient's risk factor, inaccurate recording of the timing of a blood sample
      c. Recall bias: Systematic error caused by differences in the accuracy or completeness of the recollections of study participants regarding past events or experiences
      d. Interviewer bias: Classic example: Interviews are not conducted in a uniform manner (or by the same person) for all study participants

3. Controlling for bias
    a. Design: For example, selection of study population
    b. Means of collecting data
    c. Sources of information (regarding disease and exposure)
    d. Analysis: May be difficult to interpret

E. Confounding in Study Design
1. A variable that affects the independent or dependent variable, altering the ability to determine the true effect on the measured outcome. These factors may hide or exaggerate a true association.
2. To minimize the potential for missing a confounding variable, all relevant information should be collected and evaluated.
3. Controlling for confounding
    a. During the design of a study
        i. Randomization
        ii. Restriction
        iii. Matching
    b. Analysis
        i. Stratification
        ii. Multivariate analysis

F. Factors Important in Assessing Causality:
1. Temporality: Cause before effect
2. Strength: Plausibility increases with strength of relationship
3. Biological gradient: Dose-response?
4. Consistency: Observations over several settings
5. Specificity: Single cause for effect
6. Plausibility: Biologically plausible
7. Coherence: Consistency with existing knowledge
8. Analogy: Preclinical expectation applied to clinical testing
9. Experiment: Randomized controlled trials

III. CASE REPORTS/CASE SERIES

A. Document and Describe Experiences, Novel Treatments, and Unusual Events. Allows hypothesis generation that can be tested with other study designs. Note that the title does not state "study."
1. Possible adverse drug reactions in one or more patients: Example: QT-interval prolongation associated with fluoroquinolone antibiotics
2. Case report: One patient
3. Case series: More than one patient with a similar experience or many case reports combined into a descriptive review
4. Reports should provide sufficient detail to allow readers to recognize same/similar cases at their center/practice.

B. Advantages and Disadvantages
1. Advantages: Hypotheses are formed, which may be the first step in describing an important clinical problem. Easy to perform and inexpensive
2. Disadvantages: Does not provide explanation other than conjecture and does not establish causality or association

IV. OBSERVATIONAL STUDY DESIGNS

A. Design Does Not Involve Investigator Intervention, Only Observation. It is essential to remember that observational study designs investigate associations—not, in most cases, causes.

B. Case-Control Study: Study Exposure in Those with and without the Outcome of Interest

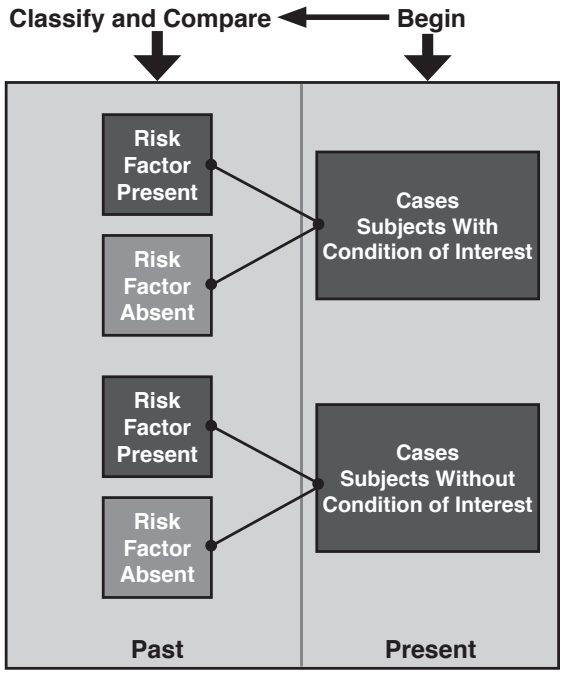

Figure 2. Case-control study design.

1. Determine the association between exposures/risk factors and disease/condition. Classic example: Aspirin use and Reye syndrome
2. Retrospective studies
3. Useful method (and perhaps the only practical way) to study exposures in rare diseases or diseases that take long periods to develop
4. Critical assumptions to minimize bias
   a. Cases are selected to be representative of those who have the disease.
   b. Controls are representative of the general population that does not have the disease and are as identical as possible to the cases, minus the presence of the disease.
   c. Information is collected from cases and controls in the same way.
5. Examples
   a. Risk of myocardial infarction associated with antihypertensive drug therapies (JAMA 1995;274: 620-5)
      i. Purpose of the study: To estimate the association between myocardial infarction (MI) and use of antihypertensives
      ii. Disease: Myocardial infarction. Exposure: Antihypertensives
      iii. Cases (n=623): Hypertensive patients who sustained a first fatal or nonfatal MI. Controls (n=2032): Patients with hypertension matched for age, sex, and calendar year. All 623 cases and 2032 controls had pharmacologically treated hypertension.
      iv. Data collection: Review of medical record; telephone interview of consenting survivors. Exposure (antihypertensive therapy) was assessed using the computerized pharmacy database.

b. Phenylpropanolamine (PPA) and the risk of hemorrhagic stroke (N Engl J Med 2000;343:1826-32). Purpose of study:
   i. To estimate in women the association between hemorrhagic stroke and the use of appetite suppressants containing PPA
   ii. To estimate the association between any use of PPA (in appetite suppressant or cough or cold remedy) and hemorrhagic stroke
   iii. To estimate in men and women the association between hemorrhagic stroke and the type of exposure to PPA
   iv. Disease: Hemorrhagic stroke (several types). Exposure: PPA
   v. Cases: Symptomatic subarachnoid or intracerebral hemorrhage (n=702). Controls: Matched by sex, race, and age (n=1376)
   vi. Exposure assessed by structured questionnaire, product photographs, and ingredient confirmation

6. Advantages
   a. Inexpensive and can be conducted quickly
   b. Allows investigation of several possible exposures or associations
7. Disadvantages
   a. Confounding must be controlled.
   b. Observational and recall bias: Looking back to recall exposures and their possible levels of exposure
   c. Selection bias: Case selection and control matching are difficult.
8. Measure of association: OR (odds ratio): In some cases, this can be an estimate of the relative risk or risk ratio (RR). The OR is interpreted as the odds of exposure to a factor in those with a condition or disease compared with those who do not have the condition or disease. Interpretation of these concepts will be presented below.

C. Cohort Study
   1. Determines the association between exposures/factors and disease/condition development. Allows an estimation of the risk of outcome (and the RR between the exposure groups). Study outcome of interest in those with and without the exposure of interest. Classic examples follow:
      a. Framingham Study. A "cohort" of subjects from Framingham, Massachusetts, were (and are) studied over time to evaluate the relationship between a variety of conditions (exposures) on the development of cardiovascular disease.
      b. Nurses' Health Study: Investigated the potential long-term consequences of the use of oral contraceptives
   2. Describes the incidence or natural history of a disease/condition and measures it in time sequence
   3. Retrospective (historical): Begins and ends in the present but involves a major backward look to collect information about events that occurred in the past

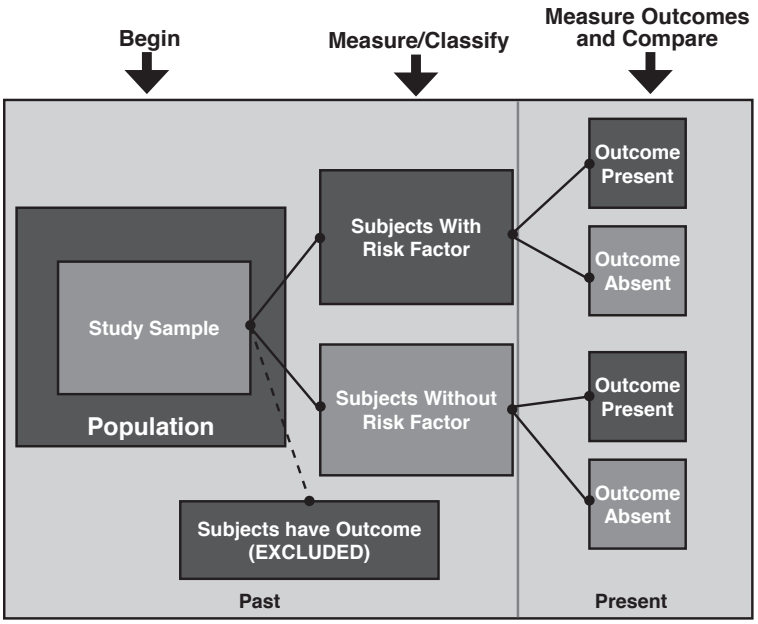

Figure 3. "Retrospective" (historical) cohort study design.

a. Advantages: Less expensive and time-consuming; no loss to follow-up, ability to investigate issues not amenable to a clinical trial or ethical or safety issues
b. Disadvantages: Only as good as the data available, little control of confounding variables through nonstatistical approaches, recall bias

4. Prospective or longitudinal: Begin in the present and progress forward, collecting data from subjects whose outcomes lie in the future

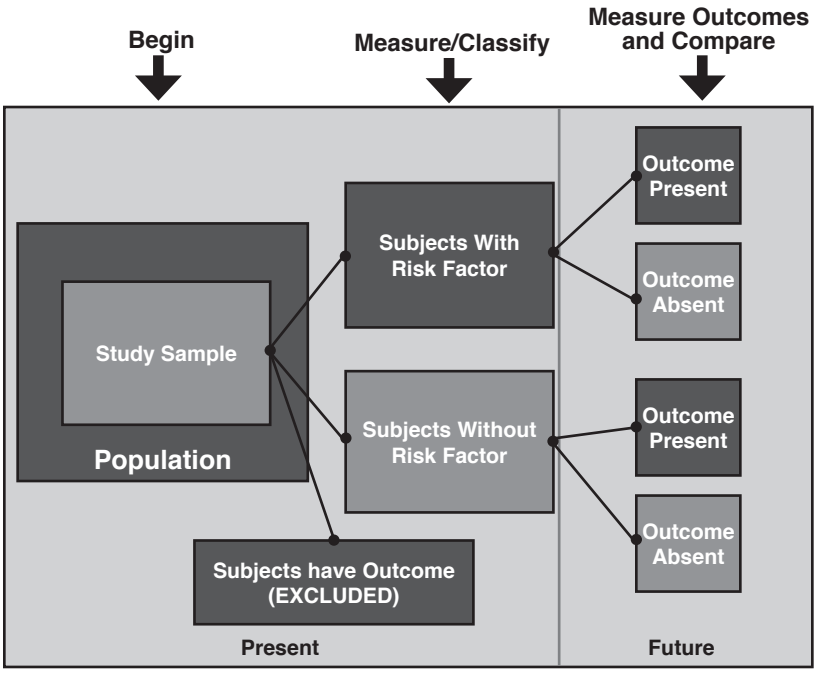

Figure 4. Prospective cohort study design.

a. Example: Prospective, observational study: Postmenopausal hormone use and secondary prevention of coronary events in the Nurses' Health Study (Ann Intern Med 2001;135:1-8)
b. Advantages: Can control for confounding factors to a greater extent, easier to plan for data collection
c. Disadvantages: More expensive and time-intensive, loss of subject follow-up, difficult to study rare diseases/conditions at a reasonable cost

5. Measure of association: Relative risk or risk ratio (RR): The risk of an event or development of a condition relative to exposure; the risk of someone developing a condition when exposed compared with someone who has not been exposed

D. Cross-sectional (a.k.a. prevalence study)
1. Identify the prevalence or characteristics of a condition in a group of individuals.
2. Examples
a. Population-based, cross-sectional study: Prevalence of serious eye disease and visual impairment in a north London population (BMJ 1998;316:1643-7)
b. Cross-sectional analysis of data from a large cohort study: Maternal characteristics and migraine pharmacotherapy during pregnancy (Cephalgia 2009;29:1267-76)
3. Advantages: Easy design, "snapshot in time," all data collected at one time, studies are accomplished by questionnaire, interview, or other available biomedical information (e.g., laboratory values)
4. Disadvantages: Does not allow the study of a factor (or factors) in individual subjects over time, just at the time of assessment; difficult to study rare conditions

V. INCIDENCE, PREVALENCE, RELATIVE RISK/RISK RATIOS, ODDS RATIOS, AND HAZARD RATIOS

A. Incidence
1. Measure of the probability of developing a disease
2. Incidence rate: Number of new cases of disease per population in a specified time
3. Calculated by dividing the number of individuals who develop a disease during a given period by the number of individuals who were at risk of developing a disease during the same period

B. Prevalence
1. Measure of the number of individuals who have a condition/disease at any given time
2. Point prevalence: Prevalence on a given date
3. Period prevalence: Prevalence in a period (e.g., year, month)

C. Interpreting RRs/ORs/HRs
1. Estimate the magnitude of association between exposure and disease. Key point: For observational studies, this is not cause and effect; it is an association.
2. The incidence of disease in the exposed group divided by the incidence of disease in the unexposed group
3. The RR cannot be directly calculated for most case-control studies; instead, the OR is usually an estimate of the RR. The RR can, however, be calculated for prospective studies.
4. The RR, OR, and HR are interpreted on the basis of their difference from unity (1.0). If the 95% CI includes unity, no statistical difference is indicated. The CI also gives us an idea of the spread within which the true effect lies. When interpreting ratios, the point of unity (no difference) is 1.0. For non-ratio outcomes, the point of unity is 0 or, for noninferiority trials, the noninferiority margin.

5. Interpretation of the index of risk, including RR, OR, and HR
   a. Direction of risk

Table 1. Direction of Risk Associated with OR and RR

RR	OR	Interpretation
< 1	< 1	Negative association RR: Risk of disease is lower in the exposed group OR: Odds of exposure is lower in the diseased group
= 1	= 1	No association RR: Risk of disease in the two groups is the same OR: Odds of exposure in the two groups is the same
> 1	> 1	Positive association RR: Risk of disease is greater in the exposed group OR: Odds of exposure is greater in the diseased group

OR = odds ratio; RR = relative risk/risk ratio.

   b. Magnitude of risk

Table 2. Magnitude of Risk Associated with OR and RR

RR	OR	Interpretation
0.75	0.75	25% reduction in the risk/odds
1.0	1.0	No difference in risk/odds
1.5	1.5	50% increase in the risk/odds
3.0	3.0	3-fold (or 200%) increase in the risk/odds

OR = odds ratio; RR = relative risk/risk ratio.

6. Calculating RR/OR/contingency tables

Table 3. Contingency Table for Estimating RR and OR

		Disease?	
		Yes	No
Exposure?	Yes	A	B
	No	C	D

a. $RR = \frac{A/(A+B)}{C/(C+D)}$

b. $OR = \frac{\frac{A}{C}}{\frac{B}{D}}$ or = (A x D)/(B x C)

7. Example (PPA study): N Engl J Med 2000;343:1826-32

Table 4. Contingency Table

		Disease? Hemorrhagic Stroke in Women	
		Yes	No
Exposure? Appetite suppression use	Yes	6	1
	No	377	749

From: Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine (PPA) and the risk of hemorrhagic stroke. N Engl J Med 2000;343:1826-32.

a. OR = (6/377)/(1/749) = 12
b. Data from the PPA study above related to appetite suppressant and development of hemorrhagic stroke

Table 5. Use of PPA and Appetite Suppressants and the Risk of Developing Hemorrhagic Stroke

	Cases (+ hemorrhagic stroke) n=383	**Controls** (− hemorrhagic stroke) n=750	**Adjusted OR** (95% CI)
Appetite suppressant: Women	6	1	16.6 (1.51–182)
Appetite suppressant: Men	0	0	—
Appetite suppressant: Either	6	1	15.9 (1.38–184)
PPA: Women	21	20	1.98 (1.00–3.90)
PPA: Men	6	13	0.62 (0.20–1.92)
PPA: Either	27	33	1.49 (0.84–2.64)

CI = confidence interval; OR = odds ratio; PPA = phenylpropanolamine.

c. What do these numbers mean?
d. Can you interpret the point estimate and 95% CI in all cases?
    i. What does the point estimate mean?
    ii. What does the CI mean?
    iii. Which ones are statistically significant?

D. Causation
1. REMEMBER: In general, we do not prove or show causality with observational studies, but there is some general "guidance" to consider when evaluating them. It is important to recognize that, in many situations, the conduct of studies to establish causality is not possible, practical, or ethical.
2. Questions used to evaluate causality
    a. Was statistical significance observed?
    b. What was the strength of the association, as measured by the OR or the RR?
    c. Were dose-response relationships evaluated?
    d. Was there a temporal relationship between exposure and disease/outcome?
    e. Have the results been consistently shown?
    f. Is there biologic plausibility to the association?
    g. Is there any experimental (e.g., animal, in vitro) evidence?

VI. RANDOMIZED CONTROLLED TRIAL DESIGN

A. Characteristics
   1. Experimental or interventional, investigator makes intervention and evaluates cause and effect. Examine etiology, cause, efficacy, using comparative groups.
   2. Some previous background information or studies should exist to suggest that the intervention used will likely be beneficial.
   3. Design allows assessment of causality.
      a. Sufficient cause
      b. Necessary cause
      c. Risk factor
   4. Minimizes bias through randomization and/or stratification
      a. Randomization
      b. Block randomization
      c. Stratification
      d. Cluster randomization
   5. Treatment controls
      a. Placebo controlled
      b. Active controlled
      c. Historical control
   6. Blinding methods
      a. Single-blind: Either subjects or investigators are unaware of subject assignment to active/control.
      b. Double-blind: Both subjects and investigators are unaware of subject assignment to active/control.
      c. Triple-blind: Both subjects and investigators are unaware of subject assignment to active/control; in addition, an analysis group is unaware.
      d. Double-dummy: Two placebos necessary to match active and control therapies
      e. Open-label: Everyone is aware of subject assignment to active/control.
   7. May use parallel or crossover design (see additional information below)
      a. Crossover provides practical and statistical efficiency.
      b. Crossover is not appropriate for certain types of treatment questions (e.g., effect of treatment on a disease that worsens quickly over time or worsens during the study period).
   8. Factorial design: Designed to answer two separate research questions in a single group of subjects
   9. Examples
      a. Clinical trial: Comparison of two drugs, comparison of two behavioral modifications, etc.
      b. Educational intervention: Online course versus lecture class format
      c. Health care intervention: Pharmacist-based health care team versus non–pharmacist-based health care team

B. Randomized Controlled Trial: Parallel Design

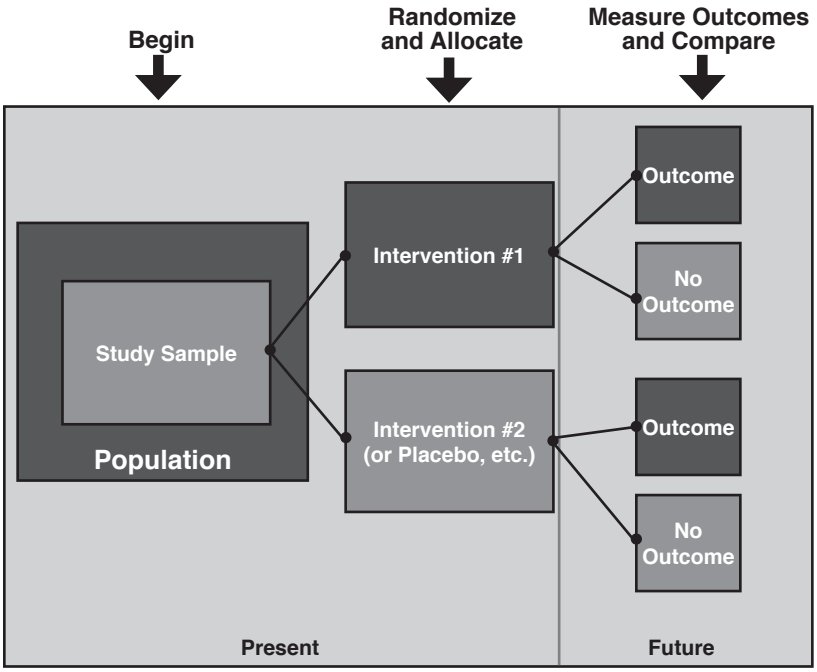

Figure 5. Randomized controlled trial: parallel design.

C. Randomized Controlled Trial: Crossover Design

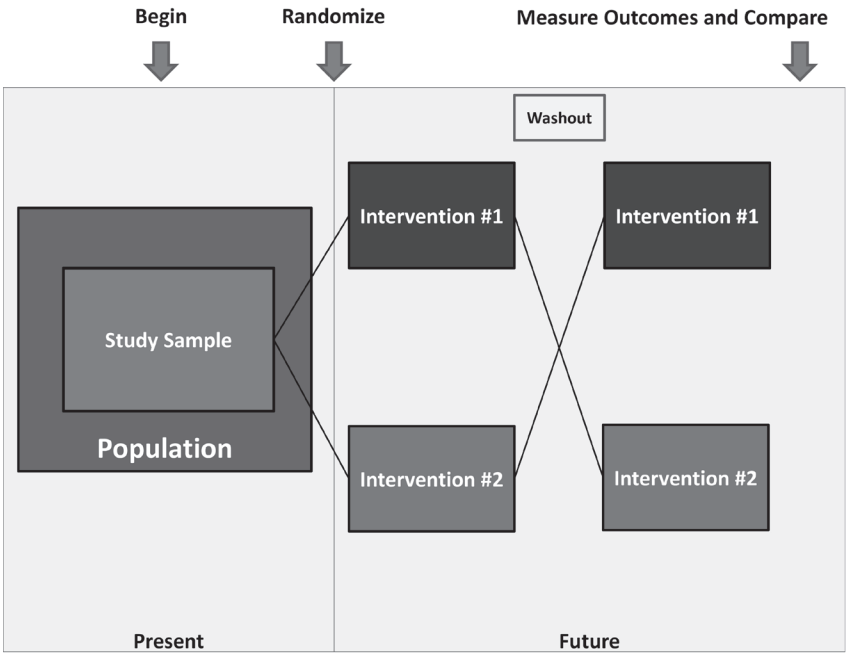

Figure 6. Randomized controlled trial: crossover design.

D. Examples of Considerations for Controlled Trials
   1. Are the results of the study valid (methods)?
      a. Did the subjects undergo randomization, and what was the randomization technique? Did the randomization process result in equal baseline characteristics?
      b. Were all subjects who entered the trial accounted for? Was follow-up complete? If not, how many were lost to follow-up, from which groups did they leave, and why?
      c. Were subjects analyzed in the groups to which they were randomized? Was intention-to-treat, per-protocol, or actual treatment analysis used?
      d. How was blinding conducted (e.g., subject, investigator), if applicable?
      e. Were the inclusion and exclusion criteria appropriate, or were they too restrictive or inclusive? Were the groups similar at the start of the trial?
      f. Was the sample size sufficient, and was a power calculation included?
      g. Were the groups handled the same way, aside from the intervention(s)?
      h. Were the statistical tests appropriate and understandable?
      i. What was assessed: Surrogate markers or true outcomes? Were *a priori* subgroup analyses performed?
   2. What were the results?
      a. How large was the treatment effect?
      b. How precise was the effect (based on CIs significant)?
      c. Did the authors properly interpret the results?
   3. Can I apply the results of this study to my patient population? Will they help me care for my patients?
      a. Can the results of this study be applied to general practice?
      b. Was a representative population studied? Can I apply this to my setting?
      c. Do the patients I care for fulfill the enrollment criteria for this study?
      d. Do the patients I care for fulfill the subgroup criteria evaluated?
      e. Do the expected benefits outweigh the expected and/or unanticipated risks?

VII. OTHER ISSUES TO CONSIDER IN CONTROLLED TRIALS

A. Subgroup Analysis
   1. Important part of controlled clinical trials (if set *a priori*)
   2. Many times, they are overused and overinterpreted, leading to unnecessary research, misinterpretation of results, and/or suboptimal patient care.
   3. Many potential pitfalls in identifying and interpreting
      a. Failure to consider several comparisons or to adjust p-values
      b. Problems with sample size (power), classification, and lack of assessment of interaction

B. Composite End Points: Often, the impression is that this practice is not a good practice.
   1. The primary end point is one of the most important decisions to make in the design of a clinical study.
   2. A composite end point combines several end points.
      a. For example, cardiovascular death, nonfatal MI, and cardiac arrest with resuscitation
      b. Usually combines measures of morbidity and mortality
      c. What does the following statement mean? Our findings show that ramipril reduces the rates of death, MI, stroke, revascularization, cardiac arrest, heart failure, complications related to diabetes, and new cases of diabetes in a broad spectrum of high-risk patients. Treating 1000 patients with ramipril for 4 years prevents about 150 events in around 70 patients.
         i. Was there a reduction in all the end points or just in some?
         ii. Are all the outcomes just as likely to occur?
         iii. Why would the investigators of this trial have been interested in all of these outcomes?

3. What are the benefits of using composite end points?
    a. No single primary outcome
    b. Alleviate problems of multiple testing
    c. Increase number of events, which decreases sample size and cost to the investigator
4. What are the limitations?
    a. Difficulties in interpreting composite end points; consider our earlier example
    b. Misattribution of statistically beneficial effects of composite measure to each of its component end points
    c. Dilution of effects, negative results for relatively common component of composite end point "hide" real differences in other end points. Undue influence exerted on composite end point by "softer" component end points
    d. "Averaging" of overall effect: Problems when component end points move in opposite directions; a sign the composite end point should be abandoned without valid conclusions being drawn
    e. Should all end points be weighed the same, or should death "weigh" more?
5. The results for each individual end point should be reported together with the results for the composite.

C. Surrogate End Points
1. Parameters thought to be associated with clinical outcomes
    a. Blood pressure and stroke prevention
    b. LDL-C reduction and cardiovascular death reduction
        i. Statins: Yes
        ii. Hormone replacement therapy: No
    c. Premature ventricular contraction suppression and reduced mortality
2. Surrogate outcomes do not always predict clinical outcomes.
3. Short-duration studies that evaluate surrogate end points may not be large enough to detect uncommon adverse events.

D. Superiority Versus Equivalence Versus Noninferiority
1. A superiority trial is designed to detect a difference between experimental treatments. This is the typical design in a clinical trial.
2. An equivalence trial is designed to confirm the absence of a meaningful difference(s) between treatments, neither better nor worse (both directions). The key is the definition of the specified margin. What difference is important? One example is a bioequivalence trial.
3. A noninferiority trial is designed to investigate whether a treatment is not clinically worse (not less effective than stated margin, [noninferiority margin] or inferior) than an existing treatment.
    a. It may be the most effective, or it may have a similar effect
    b. Useful when placebo administration is not possible for ethical reasons
    c. ONTARGET (The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial): N Engl J Med 2008;358:1547-59.
        i. Designed to evaluate telmisartan, ramipril, or their combination in patients with a high risk of vascular disease
        ii. Objective was to determine whether telmisartan was noninferior to ramipril in the incidence of cardiovascular deaths
        iii. Noninferior difference was defined as 13% or less
    d. Essentials of noninferiority design
        i. Control group must be effective
        ii. Current study similar to previous study with control and with equal doses, clinical conditions, and design used
        iii. Adequate power is essential, and usually, larger sample sizes are required.

VIII. CONTROLLED CLINICAL TRIALS: ANALYSIS

A. Controlled Clinical Trial: Application (JAMA 1998;280:605-13)
   1. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease (CHD) in postmenopausal women
   2. Objective: To determine whether estrogen plus progestin therapy alters the risk of CHD in postmenopausal women with established CHD
   3. Randomized, blinded, placebo-controlled
      a. Two treatment arms: ERT-P (conjugated equine estrogen 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day) and placebo—n=2763 with coronary artery disease, younger than 80 years; mean age 66.7 years
      b. Follow-up averaged 4.1 years; 82% of patients undergoing hormone replacement therapy still taking hormone at the end of 1 year; 75% at the end of 3 years
   4. End points
      a. Primary: Nonfatal MI or CHD death
      b. Secondary: Many, including all-cause mortality. Are these composite outcomes appropriate?
   5. Statistical analysis
      a. Baseline characteristics: t-test and chi-square: Is comparing baseline characteristics necessary in this type of trial?
      b. Power analysis and sample size calculation
      c. Kaplan-Meier with Cox proportional hazards model
   6. Surrogate end point: LDL-C lowered
   7. Results:

Table 6. Death and Secondary End Points by Treatment Group (Overall)

	ERT-P	Placebo	HR (95% CI)
Primary CHD events	12.5%	12.7%	0.99 (0.80–1.22)
CHD death	5.1%	4.2%	1.24 (0.81–1.75)
Any thromboembolic event	2.5%	0.9%	2.89 (1.50–5.58)
Gallbladder disease	6.1%	4.5%	1.38 (1.00–1.92)

CHD = coronary heart disease; CI = confidence interval; ERT-P = conjugated equine estrogen 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day; HR = hazard ratio.

   8. Significant time trend: More CHD events in the treatment group than in placebo in year 1 and fewer in years 4 and 5
   9. Author's conclusions
      a. During follow-up, ERT-P did not reduce overall rate of CHD events.
      b. Treatment increased rate of thromboembolic evens and gallbladder disease.

B. Questions to Consider in Evaluating and Interpreting a Clinical Trial
   1. Study design
      a. Was the studied sample representative of the population or the individual to whom the results were being applied?
      b. Were the inclusion/exclusion criteria appropriate, or were they overly restrictive or inclusive?
      c. Sufficient sample size, power, and so forth? Was a power analysis included?
      d. Was a study objective and/or hypothesis provided?

e. Was the study blinded and to whom? (subject, investigator, study personnel, or all?)
f. Was a run-in phase used? If so, why? Did it affect the interpretation of the trial?
g. What type of randomization method was performed? Did the randomization process produce equal baseline characteristics between all groups?

2. Outcomes/assessments
   a. Were the primary and/or secondary outcomes identified, were they reasonable, and did they apply to clinical practice?
   b. Was a composite outcome used, and were all the individual components identified and clearly stated in the methods and results?
   c. Were surrogate markers used instead of (or in addition to) clinically relevant outcomes?
3. Analysis
   a. What analysis technique was used: Intention-to-treat, as-treated, or per-protocol?
   b. Were the statistical tests appropriate?
4. Interpretation: Was the author's interpretation appropriate and within the confines of the study design?
5. Extrapolation
   a. Are you applying the results to similar patients in a similar setting?
   b. Are there possible additional adverse effects that were not measured in this study?

IX. COMMON APPROACHES TO ANALYZING CLINICAL TRIALS

A. Intention-to-Treat Analysis
   1. Compares outcomes on the basis of initial group assignment or "as randomized." The allocation to groups was how they were "intended to be treated," even though they may not have taken the medication for the duration of the study, dropped out, and did not comply with the protocol.
   2. Determines effect of treatment under usual conditions of use. Analogous to routine clinical practice in which a patient receives a prescription but may not adhere to the prescribed drug regimen.
   3. Gives a conservative estimate of differences in treatments; may underestimate treatment benefits
   4. Most common approach to assessing clinical trial results
   5. This is the preferred type of analysis in a superiority trial.

B. Per-Protocol Analysis
   1. Subjects who do not adhere to allocated treatment are not included in the final analysis; only those who completed the trial and adhered to the protocol (based on some predetermined definition [e.g., 80% adherence])
   2. Provides additional information about treatment efficacy and provides more generous estimates of differences between treatments
   3. Subject to several issues because of factors such as lower sample size and definitions of adherence. Results are more difficult to interpret and would be validly applied only to adherent patients like those in the trial; not necessarily generalizable to all patients
   4. Preferred type of analysis in noninferiority trials, although intention-to-treat analysis is often also used

C. As-Treated Analysis
   1. Subjects are analyzed by the actual intervention received. If subjects were in the active treatment group but did not take active treatment, the data would be analyzed as if they were in the placebo group.
   2. This analysis essentially ignores/destroys the randomization process for those who did not adhere to study design. Results should be interpreted with caution.

X. SYSTEMATIC REVIEW/META-ANALYSIS

A. Introduction
   1. Dramatic increase in the number of these types of papers
   2. First meta-analysis probably published in 1904: Assessment of typhoid vaccine effectiveness

B. Systematic Review
   1. Summary that uses explicit methods to perform a comprehensive literature search, critically appraise it, and synthesize the world literature on a specific topic
   2. Differs from a standard literature review: The study results are more comprehensively synthesized and reviewed.
   3. As with a controlled clinical trial (or other studies), the key is a well-documented and well-described systematic review.
   4. Differs from other reviews, which combine evaluation with opinions

C. Meta-analysis
   1. Systematic review that uses mathematical/statistical techniques to summarize the results of the evaluated studies
   2. These techniques may improve on the following:
      a. Calculation of effect size
      b. Increase in statistical power
      c. Interpretation of disparate results
      d. Reduction in bias
      e. Answers to questions that may not be addressable with individual studies
   3. Reliant on criteria for inclusion of previous studies and statistical methods to ensure validity. Details of included studies are essential.
   4. Elements of trial methodology
      a. Research question
      b. Identification of available studies
      c. Criteria for trial inclusion/exclusion
      d. Data collection and presentation of findings
      e. Calculation of summary estimate: Ideally with forest plot (Figure 7)
      f. Assessment of heterogeneity
         i. Statistical heterogeneity
         ii. χ^2 and Cochran Q are common tests for heterogeneity.
      g. Assessment of publication bias: Funnel plot
      h. Sensitivity analysis

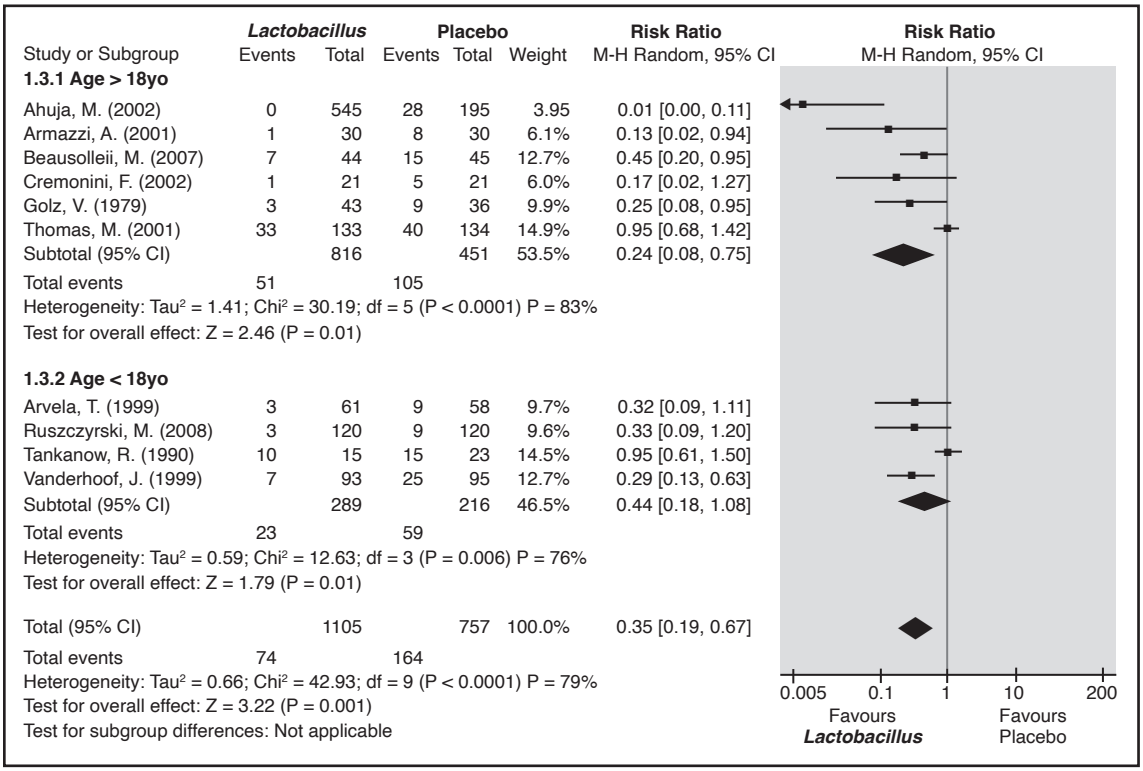
Lactobacillus
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H Random, 95% CI
M-H Random, 95% CI
1.3.1 Age > 18yo
Ahuja, M. (2002) 0 545 28 195 3.95 0.01 [0.00, 0.11]
Armazzi, A. (2001) 1 30 8 30 6.1% 0.13 [0.02, 0.94]
Beausolleii, M. (2007) 7 44 15 45 12.7% 0.45 [0.20, 0.95]
Cremonini, F. (2002) 1 21 5 21 6.0% 0.17 [0.02, 1.27]
Golz, V. (1979) 3 43 9 36 9.9% 0.25 [0.08, 0.95]
Thomas, M. (2001) 33 133 40 134 14.9% 0.95 [0.68, 1.42]
Subtotal (95% CI) 816 451 53.5% 0.24 [0.08, 0.75]
Total events 51 105
Heterogeneity: Tau² = 1.41; Chi² = 30.19; df = 5 (P < 0.0001) P = 83%
Test for overall effect: Z = 2.46 (P = 0.01)
1.3.2 Age < 18yo
Arvela, T. (1999) 3 61 9 58 9.7% 0.32 [0.09, 1.11]
Ruszczyrski, M. (2008) 3 120 9 120 9.6% 0.33 [0.09, 1.20]
Tankanow, R. (1990) 10 15 15 23 14.5% 0.95 [0.61, 1.50]
Vanderhoof, J. (1999) 7 93 25 95 12.7% 0.29 [0.13, 0.63]
Subtotal (95% CI) 289 216 46.5% 0.44 [0.18, 1.08]
Total events 23 59
Heterogeneity: Tau² = 0.59; Chi² = 12.63; df = 3 (P = 0.006) P = 76%
Test for overall effect: Z = 1.79 (P = 0.01)
Total (95% CI) 1105 757 100.0% 0.35 [0.19, 0.67]
Total events 74 164
Heterogeneity: Tau² = 0.66; Chi² = 42.93; df = 9 (P < 0.0001) P = 79%
Test for overall effect: Z = 3.22 (P = 0.001)
Test for subgroup differences: Not applicable
0.005 0.1 1 10 200
Favours Lactobacillus
Favours Placebo

Figure 7. Forest plots.

CI = confidence interval; yo = years old.

From: Kale-Pradhan PB, Jassal HK, Wilhelm SM. Role of Lactobacillus in the prevention of antibiotic-associated diarrhea: a meta-analysis. Pharmacotherapy 2010;30:119-26.

XI. SUMMARY MEASURES OF EFFECT

A. Absolute Risk Measures
   1. Absolute risk (AR): Chance of an outcome occurring
      a. Table 7 example: ARRamipril = 14.0 (%) or 0.140
      b. Table 7 example: ARPlacebo = 17.8 (%) or 0.178
   2. Absolute risk reduction (ARR): Difference in the absolute risk in exposed vs. unexposed
      a. ARR: ARunexposed – ARexposed
      b. Table 7 example: ARPlacebo – ARRamipril
      c. Table 7 example: ARR: 0.178 - 0.140 = 0.038
   3. Number needed to treat (NNT)
      a. Another means to characterize changes or differences in absolute risk
      b. Definition: The reciprocal of the absolute risk reduction (ARR)
      c. NNT = 1/(ARR)
      d. Rounded to the next-highest whole number is the most conservative approach
      e. Applied to clinical outcomes with dichotomous data (e.g., yes/no, alive/dead, MI/no MI)
      f. Assumes the baseline risk is the same for all patients (or that it is unrelated to RR)
      g. Extrapolation beyond studied time points should not occur.
      h. NNTs should be provided only for statistically significant effects.
      i. Number needed to harm depends on the outcome being addressed.

B. Relative Risk Measures
   1. Relative risk (RR): Discussed earlier. Ratio of the risk in the exposed group to the risk of the outcome in the unexposed group
   2. Relative risk reduction (RRR)
      a. RRR: (ARunexposed – ARexposed)/ARunexposed
      b. Table 7 example: (ARPlacebo – ARRamipril)/ARPlacebo
      c. Table 7 example: RRR: (0.178 – 0.140)/0.178 = 0.21 (or 21%)

C. Absolute differences are more important than relative differences, though the authors of many clinical studies highlight the differences observed in trials with relative differences because they are numerically larger. Why? Larger numbers are more convincing to practitioners and patients. Most drug advertisements (both directly to patients and to health care professionals) quote relative differences.

D. NNT application
   1. HOPE (Heart Outcomes Prevention Evaluation) study (N Engl J Med 2000;342:145-53)
   2. Study evaluated the effect of ramipril on cardiovascular events in high-risk patients.
   3. Prospective randomized double-blind study
      a. 9297 high-risk patients received ramipril or matching placebo once daily for an average follow-up of 5 years.
      b. Primary outcome: Composite of MI, stroke, or death from cardiovascular causes
   4. Results shown in Table 7.

Table 7. Risk of Primary and Secondary End Points by Treatment Group

Outcome	Absolute Risk (%) Ramipril	Absolute Risk (%) Placebo	Relative Risk	RRR	ARR	NNT
Combined	14.0	17.8	0.79	0.21	0.038	27
Death from CV causes	6.1	8.1	0.74	0.25	0.02	50
Myocardial infarction	9.9	12.3	0.80	0.20	0.024	42
Stroke	3.4	4.9	0.68	0.31	0.015	67

ARR = absolute risk reduction; CV = cardiovascular; NNT = number needed to treat; RRR = relative risk reduction.

XII. REPORTING GUIDELINES FOR CLINICAL STUDIES

A. The Consolidated Standards of Reporting Trials (CONSORT)
   1. Initially published in 1996 and updated several times since—most recently, in 2010
   2. Created in an effort to improve, standardize, and increase the transparency of the reporting of clinical trials and to facilitate the improvement of literature evaluation
   3. Available at www.consort-statement.org/
   4. The CONSORT statement has been endorsed by several publications and published in these journals.
   5. The CONSORT statement
      a. The checklist: 25-item checklist pertaining to the content of the following:
         i. Title
         ii. Abstract
         iii. Introduction
         iv. Methods
         v. Results
         vi. Discussion
         vii. Other information

b. The flow diagram: Intended to depict the passage of study participants through the randomized controlled trial

6. Extensions of the CONSORT statement
   a. Design extensions
      i. Cluster trials
      ii. Noninferiority and equivalence trials
      iii. Pragmatic trials
   b. Intervention extension
      i. Herbal medicinal interventions
      ii. Nonpharmacologic interventions
      iii. Acupuncture interventions
   c. Data extensions
      i. Patient-reported outcomes
      ii. Harms
      iii. Abstracts

B. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement
   1. Initially published in 2007
   2. "An international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal editors involved in the conduct and dissemination of observational studies"
   3. Available at www.strobe-statement.org
   4. Endorsed by several publications and published in these journals
   5. The STROBE checklist: 22-item checklist, same basic concepts as the CONSORT checklist, with alterations germane to observational trials

C. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)
   1. Established in 1996 (as QUOROM), renamed in 2009
   2. Evidence-based minimum set of items for reporting systematic reviews and meta-analyses
   3. Available at www.prisma-statement.org/
      a. The PRISMA checklist: 27-item checklist with alterations germane to systematic reviews and meta-analyses
      b. The PRISMA flow diagram: Four-stage diagram, depicting the flow of information through the systematic review
      c. The PRISMA explanation and elaboration document: Intended to enhance the use and understanding of the PRISMA statement

D. Enhancing the Quality and Transparency of Health Research (EQUATOR) Network
   1. International initiative to improve the reliability and value of medical research literature by promoting transparent and accurate reporting of research studies
   2. Does not have its own statements, but promotes the use of key reporting guidelines
   3. Many other statements regarding study types not addressed in the discussion related to CONSORT, STROBE, and PRISMA are listed on the EQUATOR network Web site (www.equator-network.org).

XIII. PHARMACOECONOMIC STUDIES

A. Cost-Minimization Analysis
   1. Differences in cost among comparable therapies are evaluated
   2. Only useful to compare therapies that have similar outcomes

B. Cost-Effectiveness Analysis
   1. Outcome: Clinical units or cost per unit health outcome (outcome examples: years of life saved, number of symptom free days, blood glucose, blood pressure, etc.)
   2. Useful to measure the cost impact when health outcomes are improved

C. Cost-Utility Analysis
   1. Assigns utility weights to outcomes so the impact can be measured in relation to cost (outcome example: quality-adjusted life-years)
   2. Compares outcomes related to mortality when mortality may not be the most important outcome

D. Cost-Benefit Analysis
   1. Monetary value is placed on both therapy costs and beneficial health outcomes.
   2. Allows analysis of both the cost of treatment and the costs saved with beneficial outcomes

XIV. SENSITIVITY/SPECIFICITY/PREDICTIVE VALUES

A. Sensitivity: Proportion of True Positives That Are Correctly Identified by a Test; a test with a high sensitivity means that a negative test can rule OUT the disorder

B. Specificity: Proportion of True Negatives That Are Correctly Identified by a Test; a test with high specificity means that a positive test can rule IN the disorder

C. Positive Predictive Value: Proportion of Patients with a Positive Test Result Who Actually HAVE the Disease

D. Negative Predictive Value: Proportion of Patients with a Negative Test Result Who Actually DO NOT HAVE the Disease

E. Example: Tables 8 and 9

Table 8. Relationship Between Test and Correct Diagnosis Identified by Disease

	Disease		
Test	**Disease Present**	**Disease Absent**	**Total**
Test positive	True positive (TP)	False positive (FP)	TP + FP
Test negative	False negative (FN)	True negative (TN)	TN + FN
Total	TP + FN	FP + TN	Total

Sensitivity = TP/(TP + FN)
Specificity = TN/(TN + FP)
Positive predictive value = TP/(TP + FP)
Negative predictive value = TN/(TN + FN)
Positive likelihood ratio = sensitivity/(1 − specificity)
Negative likelihood ratio = (1 − sensitivity)/specificity

Table 9. Relationship Between Test and Correct Diagnosis Identified by Disease in a Published Study

	Disease		
Test	**Positive disease**	**Negative disease**	**Total**
Positive	231 (true positive)	32 (false positive)	263
Negative	27 (false negative)	54 (true negative)	81
Total	258	86	344

From: Drum DE, Christacapoulos JS. Hepatic scintigraphy in clinical decision making. J Nucl Med 1972;13:908-15.

XV. INSTITUTIONAL REVIEW BOARD/HUMAN SUBJECTS' RESEARCH

A. Definitions
   1. Research: Systematic investigation (i.e., research development, testing, and evaluation) designed to develop or contribute to generalizable knowledge
   2. Human subject: Living individual about whom an investigator obtains data through intervention or interaction with the individual OR identifiable private information
   3. Quality improvement versus research
      a. In general, if the results of a project are presented outside an organization (i.e., contributes to generalized knowledge), either as a publication or a presentation, it is defined as research.
      b. If the results of a project are to be used internally and are not meant to contribute to generalized knowledge, the activities will fall under quality improvement. Ideally, the IRB makes this decision.

B. History and Development of Research Ethics
   1. Nuremberg Code (1948)
      a. Subjects should give informed voluntary consent.
      b. The benefits of research must outweigh the risks.
   2. Declaration of Helsinki (1964)
      a. Governs international research ethics
      b. Defines rules for "research combined with clinical care" and "nontherapeutic research"
      c. Basis for good clinical practices used today
   3. Tuskegee Syphilis Study (1932–1972)
      a. The study did not minimize risks to human subjects. In fact, it increased their risks.
      b. These issues heightened awareness of the need to protect human subjects and to ensure their informed voluntary consent.
   4. Belmont Report (1978): Prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
      a. Summarizes the basic ethical principles identified in its deliberations, including respect for individuals, beneficence, and justice
      b. Serves as a statement of basic ethical principles and guidelines that assist in resolving the ethical problems that surround the conduct of research with human subjects
   5. Code of Federal Regulations (CFR) (1981): The Department of Health and Human Services (DHHS) and the U.S. Food and Drug Administration (FDA) issued regulations according to the Belmont Report:
      a. DHHS: CFR Title 45 (public welfare), Part 46 (protection of human subjects)
      b. FDA: CFR Title 21 (food and drugs), Parts 50 (protection of human subjects) and 56 (IRBs)

6. Common Rule (1991): 14 other federal departments and agencies adopted DHHS regulations under 45 CFR 46 part A. Main elements include:
    a. Obtaining and documenting informed consent
    b. IRB membership, function, operations, review of research, and recordkeeping
    c. Additional protections for certain vulnerable research subjects: Pregnant women, prisoners, children, individuals with impaired capacity
    d. Ensuring compliance by research institutions
        i. All institutions that conduct federally sponsored research must provide the federal government "assurance" that states the institution's principles for protecting the rights and welfare of human subjects.
        ii. Multiple project assurance is the most common approach to this.
7. Revised Common Rule (a.k.a. the Final Rule [TFR]) (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html):
    a. Revisions to the Common Rule to better protect human subjects in research while better facilitating valuable research
    b. Includes even more federal departments and agencies
    c. Published January 19, 2017; went into effect July 19, 2018
    d. Main elements of TFR:
        i. Improved consent form requirements
        ii. One IRB approval for multi-site studies
        iii. New exempt categories
        iv. Less ongoing review
8. IRB review of studies: Reviewed at one of three levels, depending on the level of risk to the human subjects. The federal guidelines that define the categories of review, which are as follows:
    a. Exemption from full IRB review
        i. Categories
            (a) Research conducted in established or commonly accepted educational settings
            (b) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior
            (c) Research involving the collection or study of existing data, documents, records, pathologic specimens, or diagnostic specimens if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects
            (d) Research and demonstration projects that are conducted by or subject to the approval of department or agency heads
        ii. Projects are not assigned an expiration date.
        iii. The IRB makes the final decision on exemption; a staff member usually reviews the proposal.
        iv. Review usually takes a few days, depending on workload.
    b. Expedited IRB review
        i. Minimal risk (no more than risk subject encounters in daily life) to participant
        ii. Minor change to previously approved study
        iii. Chairperson or designee reviews the proposal.
        iv. Review usually takes a few weeks, depending on workload.
    c. Full IRB review: More than minimal risk
        i. Review protocol and supporting documents.
        ii. Lengthy process, usually months
        iii. Full IRB reviews the proposal.

Table 10. Examples of IRB Review Categories

Type of Review	Examples
Exemption from review	Epidemiologic study with NHANES data Study of changes in the number of days requiring antibiotics, using de-identified institutional data
Expedited review	Cross-sectional study of patients with heart failure measuring a biomarker, requiring a single blood sample Case-control study of the relationship between admission to the hospital and drug use
Full review	Randomized controlled trial of a new drug or device for heart failure therapy Cross-sectional study requiring bronchoscopy after administration of methacholine

IRB = institutional review board; NHANES = National Health and Nutrition Examination Survey.

9. IRB composition
    a. At least five members
        i. Chairperson
        ii. Scientific member
        iii. Nonscientific member
        iv. Layperson unaffiliated with the institution
        v. Practitioner
    b. Sufficient qualifications through the experience, expertise, and diversity of its members and backgrounds, including considerations of their racial and cultural heritage and their sensitivity to issues such as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects
    c. Membership must be able to ensure protection of vulnerable populations.
    d. Membership must come from more than one profession.
10. Informed consent
    a. Informed consent is a process, not just a form. Information must be presented to the individual (or representative) to enable that person to make a voluntary decision to participate as a research subject.
    b. Components
        i. Description of any reasonably foreseeable risks or discomforts
        ii. Description of any benefits to the subject or to others that may reasonably be expected
        iii. Disclosure of appropriate alternative procedures or courses of treatment, if any
        iv. Statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
        v. For research involving more than minimal risk, an explanation about whether any compensation and an explanation about whether any medical treatments are available if injury occurs
        vi. Contact information for answers to questions about the research and research subjects' rights; whom to contact if the subject has a research-related injury
        vii. A statement that participation is voluntary; refusal to participate will involve no penalty or loss of benefits, and the subject may discontinue participation at any time without penalty

c. Waiver or alteration of consent: An IRB may waive/alter informed consent if the following are met:
   i. No more than minimal risk
   ii. Will not adversely affect the rights and welfare of the subjects
   iii. The research could not practicably be carried out without waiver.
   iv. Subjects will be provided additional pertinent information after participation.
d. An IRB may also waive informed consent in a limited class of research in emergency settings.
e. New required elements for informed consent regarding collection of identifiable information or identifiable specimens
   i. Consent must state that unspecified future research may occur OR that information or biospecimens will not be used for future research.
   ii. New required section of consent
      (a) Key information must be presented first.
      (b) For clinical trials, one IRB-approved consent form must be posted on a publicly available website.
      (c) Waiver of documentation of consent: New additional exception for subjects when signing the consent form is not the cultural norm

XVI. PROFESSIONAL WRITING: THE PUBLICATION PROCESS

A. Primary Literature
   1. Experimental studies
   2. Observational studies
   3. Descriptive reports
   4. Quasi-experimental

B. Publication Process
   1. Journal selection
      a. Topic
      b. Journal quality
         i. Impact factor
         ii. Immediacy index
      c. Open access
   2. Preparation of submission: Paper parts
      a. Title page
      b. Abstract
      c. Introduction/background
      d. Methods
      e. Results
      f. Discussion
   3. Editorial and peer review
      a. Types of reviews
         i. Single-blind review: The reviewer's identity is hidden from the author, but the reviewer knows the author.
         ii. Double-blind review: Both reviewer and author are blinded.
         iii. Open review: Reviewer and author are known to each other.
         iv. Published review: Reviewers' comments are published together with the paper.

   b. Role of reviewer
      i. Does the scientific content have value and originality?
      ii. Is the paper consistent with journal guidelines?
      iii. Are the methods appropriate?
      iv. What changes should be made or additional experiments conducted?
      v. Make a recommendation (accept, revise, reject) to the editor.
4. Revision process
5. Poor-quality research, why?
   a. Academic scientists need to publish.
   b. Poor training or investigators/writers
   c. Lack of reviewers with sufficient knowledge or time to review
   d. Least publishable unit: Several publications from same study
   e. Other influences
      i. Current political issues and hot topics
      ii. Industry
         (a) Design and funding of studies
         (b) Comments during publication stage
         (c) Ghost writers
         (d) Promotional activities

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ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B
Recall bias is always a potential concern for case-control studies because of the amount of time that passes between the study and the drug "ingestion." Because risk factors were not included in the study design, this is of concern (Answer B is correct). Although a study may be susceptible to many types of bias, the other choices would not pose as much risk (if any) compared with recall bias (Answers A, C, and D are incorrect).

2. Answer: B
Internal validity is greatly jeopardized because the study is not designed to protect against this possible bias. In a sense, this design flaw jeopardizes external validity (how well does a study apply to other patients with this condition/disease?), but a lack of internal validity is most affected (Answer B is correct). The other answers can be adequately controlled for in the design and conduct of the study (Answers A, C, and D are incorrect).

3. Answer: B
Intention-to-treat analysis generally considers the approach, which gives the best estimate of use effectiveness (use under typical clinical trial conditions), whereas per-protocol analysis gives a better estimate of method effectiveness (use under ideal conditions) (Answer B is correct; Answer C is incorrect). Intention-to-treat analysis is the most common approach to data analysis for randomized controlled trials and may underestimate the treatment effect (Answer D is incorrect). Recall bias is not a concern with randomized controlled trials (Answer A is incorrect).

4. Answer: B
The CI of the difference in recurrence rate between the two groups includes zero; thus, there is no statistically significant difference between the two groups (Answer B is correct). Answer A is incorrect because the 95% CI contains zero and is therefore not statistically significant. Answer C is incorrect because not enough information is provided. Answer D is incorrect because all the above information can be determined without the benefit of reported p-values.

5. Answer: D
Answers A and C are incorrect calculations. Calculating the NNT to prevent one recurrence using twice-daily therapy is as follows: $0.044 - 0.029 = 0.015$ and $1/0.015 = 66.7\ldots67$; however, the NNT should not be calculated when the end point of interest is nonsignificant (Answer B is incorrect; Answer D is correct).

6. Answer: C
Answers A and B are incorrect because the margarine with ALA did not significantly reduce the risk of cardiovascular events (the 95% CI includes 1 [no difference in risk]). Answer D is incorrect because the p-value is not required for interpreting statistical significance when the 95% CI is provided. Answer C is correct because the p-value corresponds to the 95% CI.

7. Answer: A
Clinical trials are usually adequately powered to compare primary end points (Answer A is correct). Because Answer B is part of the composite outcomes, the study was likely not powered to detect this outcome independently. Similarly, even though the subgroup analysis was determined a priori, the study is not typically designed to have sufficient power to make this comparison (Answers C and D are incorrect).

8. Answer: D
Answers A and B are incorrect because each implies that one drug is more effective than the other. In this type of study design, neither drug is more/less effective. Answer C is incorrect because the CI of the OR does not include 1; thus, the finding is statistically significant at the 5% level, making Answer D correct.

9. Answer: A
Federal law guidance for IRB membership simply states that membership must include at least five individuals: a chairperson, a scientific member, a nonscientific member, a layperson unaffiliated with the institution, and a practitioner (Answer A is correct). There is no requirement for size of membership other than for five or a certain number of types of individuals (Answers B and C are incorrect) or for a physician (Answer D is incorrect).

10. Answer: B

Answer A is incorrect because information related to how the selection of research participants occurred should be in the methods. The results/summary of previous studies (Answer B) are found in the introduction to the study to frame the objective of the current study or in the discussion to relate the results of the current study to the results of other studies. Answer C is incorrect because this information should be in the results section. Answer D is incorrect because acknowledgments should be contained in the acknowledgment section.

Chronic Care in Cardiology

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Chronic Care in Cardiology

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Learning Objectives

1. Recommend patient-specific pharmacologic therapy for the management of chronic heart failure, with an emphasis on mortality-reducing agents and their target doses.
2. Develop an evidence-based pharmacologic regimen and monitoring plan for patients with atrial fibrillation.
3. Develop an optimal pharmacologic management plan for a patient with hypertension according to practice guidelines and clinical trial evidence.
4. Design an appropriate dyslipidemia regimen on the basis of a patient's atherosclerotic cardiovascular disease (ASCVD) risk.
5. Determine the appropriate pharmacologic therapy for patients with stable coronary heart disease.

Abbreviations in This Chapter

ACC/AHA	American College of Cardiology/ American Heart Association
ACCP	American College of Chest Physicians
ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
ARA	Aldosterone receptor antagonist
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
ASCVD	Atherosclerotic cardiovascular disease
AV	Atrioventricular
BNP	Brain natriuretic peptide
BP	Blood pressure
CCB	Calcium channel blocker
CHD	Coronary heart disease
CK	Creatine kinase
CKD	Chronic kidney disease
CO	Cardiac output
CV	Cardiovascular
CYP	Cytochrome P450
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
DHA	Docosahexaenoic acid
DHP	Dihydropyridine
DM	Diabetes mellitus
DOAC	Direct oral anticoagulant
ECG	Electrocardiogram
EPA	Eicosapentaenoic acid
GI	Gastrointestinal
HDL-C	High-density lipoprotein-cholesterol
HF	Heart failure
HF*p*EF	Heart failure with preserved ejection fraction
HFrecEF	Heart failure with recovered ejection fraction
HF*r*EF	Heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
HoFH	Homozygous familial hypercholesterolemia
HR	Heart rate
HRS	Heart Rhythm Society
HTN	Hypertension
INR	International normalized ratio
K	Potassium
LDL-C	Low-density lipoprotein-cholesterol
LFTs	Liver function tests
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
Na	Sodium
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
P-gp	P-glycoprotein
PAD	Peripheral arterial disease
PCE	Pooled Cohort Equation
REMS	Risk Evaluation and Mitigation Strategy
SA	Sinoatrial
SBP	Systolic blood pressure
SCr	Serum creatinine
SR	Sinus rhythm
SVR	Systemic vascular resistance
TC	Total cholesterol
TEE	Transesophageal echocardiogram
TG	Triglycerides
TIA	Transient ischemic attack

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. R.S., a 58-year-old woman with a history of hypertension (HTN), coronary heart disease (CHD), myocardial infarction (MI) 4 months ago, and dyslipidemia, presents to the clinic for a follow-up. She has no worsening signs or symptoms of dyspnea or edema compared with her baseline. An echocardiogram reveals a left ventricular ejection fraction (LVEF) of 35%. She is in New York Heart Association (NYHA) class III. Her medications include aspirin 81 mg/day, metoprolol succinate

150 mg/day, and atorvastatin 40 mg every night. Her vital signs include blood pressure (BP) 138/80 mm Hg and heart rate (HR) 58 beats/minute. Her lungs are clear, and laboratory results are within normal limits. Given her history and physical examination, what is the most appropriate modification to R.S.'s current drug therapy?

A. Continue current therapy.
B. Initiate digoxin 0.125 mg/day.
C. Initiate spironolactone 25 mg/day.
D. Initiate lisinopril 5 mg/day.

2. J.O. is a 64-year-old woman with NYHA class II nonischemic dilated cardiomyopathy (LVEF of 30%). She presents to the heart failure (HF) clinic for a follow-up. She is euvolemic. Her medications include enalapril 10 mg twice daily, furosemide 40 mg twice daily, and potassium chloride 20 mEq twice daily. Her vital signs include BP 130/88 mm Hg and HR 78 beats/minute. Her laboratory results are within normal limits. What is the best way to manage J.O.'s HF?

A. Continue current regimen.
B. Increase enalapril to 20 mg twice daily.
C. Initiate carvedilol 3.125 mg twice daily.
D. Initiate digoxin 0.125 mg/day.

3. J.M. is a 65-year-old woman with a history of HTN and poor medication adherence who presents to her primary care physician with shortness of breath and markedly decreased exercise tolerance. An echocardiogram reveals an LVEF of 65%, with diastolic dysfunction. J.M.'s medications include extended-release nifedipine 90 mg/day and hydrochlorothiazide 25 mg/day. Her vital signs include BP 128/78 mm Hg and HR 98 beats/minute. Her lung fields are clear to auscultation, and there is no evidence of systemic congestion. Which is the best pharmacologic management for J.M.?

A. Discontinue extended-release nifedipine and initiate diltiazem 240 mg/day.
B. Discontinue hydrochlorothiazide and initiate furosemide 40 mg twice daily.
C. Initiate digoxin 0.125 mg/day.
D. Add lisinopril 5 mg/day.

4. B.W. is a 78-year-old man with a history of HTN, peripheral arterial disease (PAD), gastroesophageal reflux disease, and asymptomatic atrial fibrillation (AF) for the past month. His therapy includes aspirin 325 mg/day, lansoprazole 30 mg every night, atenolol 50 mg/day, lisinopril 10 mg/day, and atorvastatin 20 mg/day. His vital signs include BP 132/72 mm Hg and HR 68 beats/minute. Which is the best therapy for B.W. at this time?

A. Add diltiazem and warfarin.
B. Add digoxin and increase lisinopril to 20 mg/day.
C. Discontinue atorvastatin and add warfarin.
D. Add warfarin and decrease aspirin to 81 mg/day.

5. Z.G. is a 61-year-old man with AF, HTN, and dyslipidemia. His medications include digoxin 0.125 mg/day, warfarin 5 mg/day, amlodipine 10 mg/day, and pravastatin 20 mg every night. He comes to the clinic with no complaints except for palpitations and shortness of breath when doing yard work. His vital signs include BP 138/80 mm Hg and HR 100 beats/minute. His international normalized ratio (INR) is 2.4, and his digoxin concentration is 1.1 ng/mL. All other laboratory results are within normal limits. Which is the best option to help with Z.G.'s symptoms?

A. Add metoprolol succinate 50 mg/day.
B. Increase digoxin to 0.25 mg/day.
C. Add verapamil 240 mg/day.
D. Continue current regimen and advise the patient to avoid activities that cause signs or symptoms.

6. R.P. is an 69-year-old African American man with a history of HTN and gout. His medications include allopurinol 300 mg/day, amlodipine 10 mg/day, and aspirin 81 mg/day. His vital signs include BP 145/85 mm Hg and HR 82 beats/minute. His laboratory values are normal and his 10-year ASCVD risk is 22.4%. Which is the best therapy for R.P.?

A. Add hydrochlorothiazide 25 mg/day to achieve a systolic blood pressure (SBP) goal of less than 130 mm Hg.
B. Add lisinopril 40 mg/day and titrate to achieve an SBP goal of less than 140.

C. Add atenolol 50 mg/day to achieve an SBP less than 130 mm Hg.

D. Make no changes to his current medications because his SBP is at goal.

7. J.T. is a 58-year-old man who presents to his primary care provider for the first time in 10 years. He has smoked 2 packs/day for the past 30 years and takes no medication. A fasting lipid panel shows total cholesterol (TC) 222 mg/dL, low-density lipoprotein cholesterol (LDL-C) 105 mg/dL, triglycerides (TG) 330 mg/dL, and high-density lipoprotein cholesterol (HDL-C) 51 mg/dL. His vital signs include BP 140/75 mm Hg and HR 80 beats/minute. His pooled cohort equation reveals a 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 14.6%. Which would be the best pharmacologic therapy to initiate in J.T.?

   A. Initiate simvastatin 20 mg/day and gemfibrozil 600 mg twice daily.

   B. Initiate rosuvastatin 2.5 mg/day.

   C. Initiate pravastatin 20 mg/day and fenofibrate 160 mg/day.

   D. Initiate atorvastatin 20 mg/day.

8. J.S. is a 43-year-old man with HTN who presents for an annual physical examination. His family history is significant for his father having HTN. His only medication is lisinopril 10 mg/day. His BP is 145/90 mm Hg. A fasting lipid profile shows TC 238 mg/dL, TG 95 mg/dL, LDL-C 176 mg/dL, and HDL-C 43 mg/dL. His calculated 10-year ASCVD risk according to the pooled cohort equation is 3.9%. Which best describes the next step for management in J.S.?

   A. Initiate high-intensity statin therapy.

   B. Do not initiate statin therapy and reevaluate risk in 1–3 years.

   C. Initiate moderate-intensity statin therapy.

   D. Do not initiate statin therapy and reevaluate risk in 4–6 years.

9. J.C. is a 62-year-old man (height 70 inches, weight 135 kg [1 month ago 143 kg]) with a history of diabetes mellitus (DM), chronic kidney disease, bipolar disorder, CHD, and hypertriglyceridemia that, in the past, has resulted in pancreatitis. His family history is significant for his father having CHD and hypertriglyceridemia. He is not a smoker, but admits drinking a 6-pack of beer daily. Pertinent laboratory findings include a hemoglobin A1C of 11.6% and a serum creatinine (SCr) of 2.6 mg/dL. He currently takes atorvastatin 40 mg every evening, aspirin 81 mg/day, metformin 1000 mg twice daily, olanzapine 10 mg/day, metoprolol tartrate 50 mg twice daily, and coenzymeQ10 200 mg/day. His fasting lipid profile is TC 402 mg/dL, LDL-C unable to calculate, HDL-C 48 mg/dL, and TG 1500 mg/dL. His other laboratory values are within normal limits. Which best describes potential secondary causes of elevated TG concentrations that should be considered in J.C.?

   A. Obesity, poorly controlled diabetes, olanzapine, metoprolol, coenzyme Q10.

   B. Alcohol consumption, poorly controlled diabetes, weight loss, β-blockers.

   C. Obesity, calcium channel blockers, hyperthyroidism, alcohol consumption.

   D. Alcohol consumption, obesity, poorly controlled diabetes, olanzapine, metoprolol.

Questions 10 and 11 pertain to the following case.

A.M. is a 32-year-old woman with type 1 DM and HTN. Her current medication regimen is as follows: ramipril 10 mg/day, chlorthalidone 25 mg/day, amlodipine 10 mg/day, ethinyl estradiol 20 mcg/norethindrone 1 mg (for the past 2 years), and insulin as directed. Her vital signs today include BP 145/83 mm Hg, repeated BP 145/81 mm Hg; HR 82 beats/minute; height 66 inches; weight 70 kg. A.M. would prefer not to take any more drugs, if possible.

10. Which option is the best clinical plan for A.M.?

   A. No change in therapy is currently warranted.

   B. Advise weight loss and recheck her BP in 3 months.

   C. Change chlorthalidone to hydrochlorothiazide.

   D. Discuss changing her contraceptive method.

11. A.M. and her husband have decided they are ready to have children. What is the best medication option for A.M.?

A. No change in therapy is warranted.

B. Discontinue ramipril and replace with labetalol.

C. Increase chlorthalidone to 50 mg/day.

D. Discontinue all antihypertensive therapy.

12. A 66-year-old African American man (height 70 inches, weight 91 kg) with AF and CHD (non–ST-segment elevation MI and stent placement 3 years ago) presents with palpitations. Rate control therapy, including trials of β-blockers and non-dihydropyridine calcium channel blockers, has been unsuccessful in controlling his symptoms. He currently takes metoprolol succinate 50 mg/day, aspirin 81 mg/day, atorvastatin 80 mg/day, lisinopril 5 mg/day, and warfarin 4 mg/day. His laboratory results show INR 2.2, potassium 4.8 mEq/L, SCr 1.2 mg/dL. His BP is 110/70 mm Hg, and his HR is 95 beats/minute. Which is the best antiarrhythmic therapy for him?

A. Disopyramide.

B. Flecainide.

C. Propafenone.

D. Sotalol.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-specific pharmacotherapy
    a. Task 1: 1–8, 10, 11, 12, 13, 14, 17
    b. Task 2: 1–3
    c. Task 3: 1–2
    d. Task 4: 1–7
    e. Task 5: 1–3
    f. Systems and patient-care problems
        i. Atrial fibrillation
        ii. Chronic CHD and chronic stable angina
        iii. Heart failure
        iv. Hypertension
        v. Dyslipidemia
2. Domain 2: Retrieval, generation, interpretation, and dissemination of knowledge in pharmacotherapy, Task 2, Knowledge Statements 1–5
3. Domain 3: System and population-based pharmacotherapy, Task 2, Knowledge Statements 4–5

I. HEART FAILURE

Patient Cases

1. L.S. is a 48-year-old woman with alcohol-induced cardiomyopathy. Her most recent LVEF is 20%; her daily activities are limited by dyspnea and fatigue (NYHA class III). Her medications include lisinopril 40 mg daily, furosemide 40 mg twice daily, carvedilol 12.5 mg twice daily, spironolactone 25 mg/day, and digoxin 0.125 mg/day. She has been stable on these doses for the past month. Her most recent laboratory results include sodium (Na) 140 mEq/L, potassium (K) 4.0 mEq/L, chloride 105 mEq/L, bicarbonate 26 mEq/L, blood urea nitrogen 12 mg/dL, SCr 0.8 mg/dL, glucose 98 mg/dL, calcium 9.0 mg/dL, phosphorus 2.8 mg/dL, magnesium 2.0 mEq/L, and digoxin 0.7 ng/mL. She weighs 69 kg, and her vital signs include BP 112/70 mm Hg and HR 68 beats/minute. She has normal breath sounds and no pedal edema. What is the best approach for maximizing the management of her HF?
   A. Increase carvedilol to 25 mg twice daily.
   B. Increase lisinopril to 80 mg/day.
   C. Increase spironolactone to 50 mg/day.
   D. Increase digoxin to 0.25 mg/day.

2. J.T. is a 62-year-old man (height 72 inches, weight 85 kg) with a history of CHD (MI 3 years ago), HTN, depression, chronic kidney disease (CKD; baseline SCr 2.8 mg/dL), PAD, osteoarthritis, hypothyroidism, and HF (LVEF of 25%). His medications include aspirin 81 mg/day, simvastatin 40 mg every night, enalapril 5 mg twice daily, metoprolol succinate 50 mg/day, furosemide 80 mg twice daily, cilostazol 100 mg twice daily, acetaminophen 650 mg four times daily, sertraline 100 mg/day, and levothyroxine 0.1 mg/day. His vital signs include BP 120/70 mm Hg and HR 72 beats/minute. Pertinent laboratory results include K 4.1 mEq/L, SCr 2.8 mg/dL, and a thyroid-stimulating hormone of 2.6 mIU/L. His HF is stable and considered NYHA class II. What is the best approach for maximizing the management of his HF?
   A. Discontinue metoprolol and begin carvedilol 12.5 mg twice daily.
   B. Increase enalapril to 10 mg twice daily.
   C. Add spironolactone 25 mg/day.
   D. Add digoxin 0.125 mg/day.

A. Background: HF is a complex clinical syndrome caused by any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.
   1. Prevalence
      a. Affects 6.2 million Americans
      b. Prevalence increases with age
   2. Heart failure with reduced ejection fraction (HF*r*EF)
      a. Defined as a clinical diagnosis of HF and an LVEF of 40% or less
      b. Dilated ventricle
      c. Two thirds of cases are attributable to coronary heart disease (CHD).
      d. One third of cases are attributable to nonischemic cardiomyopathy.
         i. HTN
         ii. Thyroid disease
         iii. Obesity
         iv. Stress (Takotsubo)

v. Cardiotoxins
   (a) Alcohol
   (b) Cocaine
   (c) Chemotherapeutic agents
      (1) Anthracyclines
      (2) Cyclophosphamide (high dose)
      (3) Fluorouracil
      (4) Trastuzumab/pertuzumab
      (5) Mitoxantrone
vi. Myocarditis
vii. Idiopathic
viii. Tachycardia
ix. Peripartum

3. Heart failure with preserved EF (HF*p*EF)
   a. Defined as an LVEF of 50% or greater; borderline HF*p*EF is LVEF 41%–49%
   b. Accounts for about 50% (highly variable) of patients with HF
   c. Impaired ventricular relaxation and filling
   d. Normal wall motion
   e. Most common cause is HTN (60%–89%).
4. Primary symptoms
   a. Dyspnea
   b. Fatigue
   c. Edema
   d. Exercise intolerance
5. Stages and functional class of HF according to the American College of Cardiology/American Heart Association (ACC/AHA) (Table 1)

Table 1. HF Stages and Corresponding NYHA Functional Class

ACC/AHA Stage		NYHA Functional Class	
A	At high risk of HF (uncontrolled risk factors) but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	Asymptomatic HF; no limitations in physical activity caused by HF symptoms
C	Structural heart disease with prior or current symptoms of HF	I	No limitations in physical activity caused by HF symptoms
		II	Slight limitation of physical activity; asymptomatic at rest, but symptoms of HF with normal level of activity
		III	Marked limitations in physical activity because of HF symptoms; asymptomatic at rest
		IV	Symptoms of HF at rest or unable to carry out any physical activity
D	Refractory HF requiring specialized interventions	IV	Symptoms of HF at rest

ACC = American College of Cardiology; AHA = American Heart Association; HF = heart failure; NYHA = New York Heart Association.

Adapted from: 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239.

6. Goals of therapy
    a. Modify or control risk factors (e.g., HTN, obesity, DM)
    b. Manage structural heart disease
    c. Reduce morbidity and mortality
    d. Prevent or minimize Na and water retention
    e. Eliminate or minimize HF symptoms
    f. Block compensatory neurohormonal activation caused by reduced cardiac output (CO)
    g. Slow progression of worsening cardiac function

B. HF*r*EF
    1. Pharmacologic therapy (Figure 1)
        a. Diuretics
            i. Place in therapy: Indicated in patients with evidence of fluid retention (class I indication)
            ii. Short-term benefit (days)
                (a) Decreased jugular venous distension
                (b) Decreased pulmonary congestion
                (c) Decreased peripheral edema
            iii. Intermediate-term benefits (weeks to months)
                (a) Decreased daily symptoms
                (b) Increased exercise tolerance
            iv. Long-term benefits (months to years): No benefit on mortality
            v. Mechanism of action: Inhibit reabsorption of Na in the ascending limb of the loop of Henle (loops) or in the distal tubule (thiazides)
            vi. Dosing and administration considerations (Table 2)
                (a) Should be combined with guideline-directed medical therapy
                (b) Start with a low initial dose and then double the dose and titrate according to the patient's weight as needed. Bioavailability differs between oral loop diuretics and must be considered when converting from one agent to another.
                (c) If a patient has fluid overload, initiate and adjust therapy to result in 0.5-1 kg of weight loss per day (may be more aggressive in the inpatient setting).
                (d) Long-term therapy should be adjusted to maintain a euvolemic state.
                (e) A loop diuretic can be combined with another diuretic class (e.g., thiazide diuretic) for synergy, if needed.
                (f) Loop diuretics are preferred because of their greater diuretic capabilities; loop diuretics also retain efficacy with decreased renal function.
            vii. Monitoring: Monitor and replace K and magnesium as needed, especially with loop diuretics (goal with cardiovascular [CV] disease is K of 4.0 mEq/L or greater and magnesium of 2.0 mEq/L or greater to minimize the risk of arrhythmias). Monitor SCr and BUN to avoid acute kidney injury with overdiureses. Also monitor HCO_3 for metabolic alkalosis with overdiuresis.

Table 2. Diuretics and Recommended Dosing[a]

Agent	Oral Bioavailability (%)	Initial Daily Dose	Maximal Total Daily Dose (mg)	Duration of Action (hr)
Loop Diuretics (inhibit 20%–25% of sodium reabsorption)				
Furosemide[b]	10–67	20–40 mg daily or BID	600	6–8
Bumetanide[b]	80–100	0.5–1 mg daily or BID	10	4–6
Torsemide	80–100	10–20 mg daily	200	12–16
Ethacrynic acid[b]	100	25–50 mg daily or BID	200	6–8
Thiazide Diuretics (inhibit 10%–15% of sodium reabsorption)				
Hydrochlorothiazide	65–75	25 mg daily or BID	200	6–12
Metolazone	40–65	2.5 mg daily	20	12–24
Chlorthalidone	64	12.5–25 mg daily	100	24–72
Chlorothiazide[b]	30–50	250–500 daily or BID	1000	6–12

[a]Equivalent doses: furosemide 40 mg = bumetanide 1 mg = torsemide 10–20 mg = ethacrynic acid 50 mg.

[b]Available in oral and intravenous formulations.

BID = twice daily.

b. ACE inhibitors
   i. Place in therapy: Recommended in all patients with HF*r*EF and current or prior symptoms, unless contraindicated (class I indication)
   ii. Benefits
      (a) Decreased mortality (about 25%–50% relative risk reduction compared with placebo depending on severity of HF)
      (b) Decreased hospitalizations (about 30% relative risk reduction compared with placebo)
      (c) Symptom improvement
      (d) Improved clinical status
      (e) Improved sense of well-being
      (f) Notable trials: CONSENSUS (enalapril), SOLVD (enalapril), SAVE (captopril), AIRE (ramipril), and TRACE (trandolapril).
   iii. Mechanism of action
      (a) Blocks production of angiotensin II
         (1) Decreases sympathetic stimulation
         (2) Decreases production of aldosterone and vasopressin
         (3) Decreases vasoconstriction (afterload and preload)
      (b) Increases bradykinins (decreases their metabolism)
         (1) Increases vasodilatory prostaglandins
         (2) May attenuate myocardial remodeling

iv. Dosing and administration considerations
  (a) Start low and double the dose every 1–4 weeks to target dose (Table 3).
  (b) ATLAS trial comparing patients with systolic dysfunction who received low-dose lisinopril (2.5–5 mg/day) and patients who received high-dose lisinopril (32.5–35 mg/day) showed no difference in all-cause mortality or CV mortality; however, the high-dose group did have a significant 12% lower risk of death or hospitalization for any reason and 24% fewer hospitalizations for HF.
  (c) Patients may notice improvement in symptoms in several weeks.
  (d) Avoid use in patients who have experienced angioedema as the result of previous ACE inhibitor use or those who are pregnant or plan to become pregnant.
  (e) Use caution if SBP is less than 80 mm Hg, SCr is greater than 3 mg/dL, K is greater than 5.0 mEq/L, or the patient has bilateral renal artery stenosis.

v. Monitoring
  (a) Monitor SCr and K for 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients (preexisting hypotension, DM, K supplements, azotemia). SCr may rise (up to a 30% increase is acceptable) because of renal efferent artery dilation (results in a slightly decreased glomerular filtration rate). Rarely, acute renal failure occurs, especially if the patient is intravascularly depleted. Be careful to avoid overdiuresis.
  (b) Monitor BP and symptoms of hypotension (e.g., dizziness, lightheadedness).
    (1) BP may be low to begin with because of low CO.
    (2) BP = CO × Systemic vascular resistance (SVR).
    (3) In HF, as CO increases because of decreased SVR, BP may decrease slightly or remain the same.
    (4) Symptoms of hypotension are often not present with small dose increases. Remember to treat the patient, not the number.
  (c) Ninety percent of people tolerate ACE inhibitors.
    (1) Angioedema (less than 1%): Can switch to angiotensin II receptor blockers (ARBs; cross-reactivity is 2.5%) or hydralazine–isosorbide dinitrate
    (2) Cough (20%): Can switch to ARBs (less than 1%)

Table 3. ACE Inhibitors and Recommended Dosing

Drug	Starting Dosage	Target Dosage	Maximal Dosage
Captopril	6.25 mg three times daily	50 mg three times daily	50 mg three times daily
Enalapril	2.5 mg twice daily	10 mg twice daily	20 mg twice daily
Lisinopril	2.5–5 mg daily	20 mg daily	40 mg daily
Perindopril	2 mg daily	8 mg daily	16 mg daily
Ramipril	1.25–2.5 mg daily	10 mg daily	10 mg daily
Trandolapril	1 mg daily	4 mg daily	4 mg daily

Note: Fosinopril and quinapril can be used; however, they do not have the same magnitude of mortality-reducing data as listed above.
ACE = angiotensin-converting enzyme

c. Angiotensin receptor blockers
  i. Place in therapy
    (a) Recommended in patients with HF*r*EF with current or prior symptoms who are unable to take an ACE inhibitor (class I indication). Have not been proven superior to ACE inhibitors at target HF dosages.

(b) Reasonable alternative to ACE inhibitors as first-line therapy if the patient is already taking an ARB (class lla indication) or as substitute for an ACE inhibitor in patients unable to take ACE inhibitors because of cough (class I indication)
(c) Possibly considered if patient has experienced ACE inhibitor–induced angioedema (cross-reactivity 2.5%)

ii. Benefits
(a) Decreased HF-related hospitalizations and decreased death from CV causes.
(b) Notable clinical trials: CHARM-Alternative (candesartan), VALIANT (valsartan), VAL-HEFT (valsartan), and HEAAL (losartan).

iii. Mechanism of action
(a) Selectively block the binding of angiotensin II to the angiotensin I receptor
(b) Deters vasoconstriction and aldosterone-secreting effects
(c) Does not affect ACE or inhibit kinin catabolism

iv. Dosing and administration
(a) Start low and double the dose every 1–4 weeks to target dose (Table 4).
(b) Patients may notice improvement in symptoms in several weeks.
(d) Avoid use in patients who have angioedema because of previous ARB use or those who are pregnant or plan to become pregnant.
(e) Use caution if SBP is less than 80 mm Hg, SCr is greater than 3 mg/dL, K is greater than 5.0 mEq/L, or the patient has bilateral renal artery stenosis.

v. Monitoring
(a) SCr and K 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients (preexisting hypotension, DM, K supplements, azotemia)
(1) SCr may rise (up to a 30% increase is acceptable) because of renal efferent artery dilation (results in a slightly decreased glomerular filtration rate).
(2) Rarely, acute renal failure occurs, especially if the patient is intravascularly depleted (be careful to avoid overdiuresis).
(b) Monitor BP and symptoms of hypotension (e.g., dizziness, lightheadedness).
(c) Other adverse reactions
(1) Angioedema (rare)
(2) Cough (less than 1%)

Table 4. ARBs and Recommended Dosing

Drug	Starting Dosage	Target Dosage
Candesartan	4–8 mg daily	32 mg daily
Losartan	25–50 mg daily	150 mg daily
Valsartan	20–40 mg twice daily	160 mg twice daily

ARB = angiotensin receptor blocker.

d. β-blockers
i. Place in therapy: Recommended in all patients with HF*r*EF with current or prior symptoms unless contraindicated (class I indication)
ii. Benefits (when added to an ACE inhibitor)
(a) Decreased mortality (about 35% relative risk reduction compared with placebo)
(b) Decreased hospitalizations (about 25% relative risk reduction compared with placebo)
(c) Symptom improvement
(d) Improved clinical status

(e) Notable clinical trials: CIBIS II (bisoprolol), MERIT-HF (metoprolol succinate), COPERNICUS (carvedilol), and COMET (metoprolol tartrate vs. carvedilol).

iii. Mechanism of action
   (a) Blocks the effect of norepinephrine and other sympathetic neurotransmitters on the heart and vascular system
      (1) Decreases ventricular arrhythmias (sudden cardiac death)
      (2) Decreases cardiac hypertrophy and cardiac cell death
      (3) Decreases vasoconstriction and HR
   (b) Carvedilol also provides α_1-blockade.
      (1) Further decreases SVR (afterload)
      (2) Results in greater reduction in BP than metoprolol succinate

iv. Dosing and administration considerations
   (a) Only bisoprolol, carvedilol, and metoprolol succinate are recommended in HF*r*EF.
   (b) Add to existing ACE inhibitor therapy (at least at a low dose) when HF symptoms are stable and patients are euvolemic.
   (c) Should not be prescribed without diuretics in patients with current or recent history of fluid retention.
   (d) Start low and increase (double) the dose every 2 weeks (or slower, if needed) to target dose. Aim to achieve target dose in 8–12 weeks (Table 5).
   (e) Avoid abrupt discontinuation; can precipitate clinical deterioration
   (f) Might not notice improvement in symptoms for several months
   (g) Should be considered even in patients with reactive airway disease or asymptomatic bradycardia

Table 5. β-Blockers and Recommended Dosing

Agent	Starting Dosage	Target Dosage
Bisoprolol	1.25 mg daily	10 mg daily
Carvedilol	3.125 mg twice daily	25 mg twice daily[a]
Carvedilol CR	10 mg daily	80 mg daily
Metoprolol succinate[b]	12.5–25 mg daily	200 mg daily

[a]50 mg twice daily if weight > 85 kg.

[b]Few or no data exist for metoprolol tartrate.

CR = controlled release

v. Monitoring
   (a) BP, HR, and symptoms of hypotension or bradycardia (monitor in 1–2 weeks)
      (1) Significant hypotension, bradycardia, or dizziness occurs in about 1% of patients when the β-blocker is titrated slowly. If these symptoms appear, lower the dose by 50%.
      (2) Of importance, remember that higher β-blocker doses are associated with greater mortality reduction. Therefore, if hypotension alone is the problem, try reducing the ACE inhibitor (or another antihypertensive) first or scheduling one agent at bedtime and one in the morning.
   (b) Increased edema or fluid retention (monitor in 1–2 weeks)
      (1) One percent to 2% more common than with placebo (in euvolemic, stable patients)
      (2) Responds to diuretic increase
      (3) Do not increase ß-blocker dose during episodes of fluid retention after therapy initiation or dose titration.

(c) Fatigue or weakness
(1) One percent to 2% more common than with placebo
(2) Usually resolves spontaneously in several weeks
(3) May require dosage decrease or discontinuation

e. Aldosterone receptor antagonists
i. Place in therapy
(a) Recommended in patients with NYHA class II–IV with an LVEF of 35% or less to reduce morbidity and mortality unless a contraindication exists. Patients with NYHA class II should have a history of CV hospitalization or elevated brain natriuretic peptide (BNP) levels (class I indication).
(b) Recommended to reduce morbidity and mortality in patients after a myocardial infarction (MI) when they have an LVEF less than or equal to 40% with symptoms of HF or an LVEF less than 40% and DM (class I indication).
ii. Benefits of spironolactone in NYHA class III and IV HF (RALES trial)
(a) Decreased mortality (30% relative risk reduction compared with placebo)
(b) Decreased hospitalizations for HF (35% relative risk reduction compared with placebo)
(c) Improved symptoms
iii. Benefits of eplerenone (selective ARA) in NYHA class II HF (EMPHASIS-HF)
(a) Decreased composite endpoint of death from CV causes or hospitalization from HF (37% relative risk reduction compared with placebo)
(b) Decreased death from CV causes (24% relative risk reduction compared with placebo)
(c) Decreased hospitalizations for HF (42% relative risk reduction compared with placebo)
(d) Decreased mortality (24% relative risk reduction compared with placebo)
iv. Benefits of eplerenone in left ventricular dysfunction after MI (EPHESUS)
(a) Decreased mortality (15% relative risk reduction compared with placebo)
(b) Decreased composite endpoint of death from CV causes or hospitalization for CV events (13% relative reduction compared with placebo)
v. Mechanism of action
(a) Blocks effects of aldosterone in the kidneys, heart, and vasculature
(b) Decreases K and magnesium loss; decreases ventricular arrhythmias
(c) Decreases Na retention; decreases fluid retention
(d) Eliminates catecholamine potentiation; decreases BP
(e) Blocks direct fibrotic actions on the myocardium
vi. Dosing and administration considerations
(a) Should be added to ACE inhibitor (or ARB) and β-blocker therapy
(b) SCr should be less than 2.5 mg/dL for men and less than 2.0 mg/dL in women (or estimated glomerular filtration rate greater than 30 mL/minute/1.73 m^2), and K should be less than or equal to 5.0 mEq/L (Table 6).
(c) In the absence of hypokalemia (K less than 4.0 mEq/L), supplemental K is not recommended when taking an ARA

Table 6. ARAs and Recommended Dosing

	eGFR ≥ 50 mL/min/1.73 m^2		**eGFR 30-49 mL/min/1.73 m^2**	
	Initial dose	**Maintenance dose**	**Initial dose**	**Maintenance dose**
Eplerenone	25 mg daily	50 mg daily	25 mg every other day	25 mg daily
Spironolactone	12.5–25 mg daily	25 mg daily or BID	12.5 mg daily or every other day	12.5–25 mg daily

ARA = aldosterone receptor antagonist; BID = twice daily; eGFR = estimated glomerular filtration rate

vii. Monitoring
  (a) K and SCr within 2–3 days, again at 7 days after starting therapy, monthly for first 3 months, and every 3 months thereafter. If the dose of ACE inhibitor or ARB is increased, restart monitoring.
    (1) Hyperkalemia was reported in only 2% of the patients in trials; however, in practice, it occurs in about 20% of patients.
    (2) Decrease dose by 50% or discontinue if K is greater than 5.5 mEq/L.
  (b) Gynecomastia
    (1) Spironolactone: Reported at a rate of 10% in clinical trials
    (2) Eplerenone can be considered as an alternative to spironolactone if gynecomastia is present.

f. Digoxin
  i. Place in therapy: Can be beneficial in decreasing hospitalizations in patients with HF*r*EF (class IIa indication); should be added after guideline-directed medical therapy
  ii. Benefits
    (a) Improved symptoms
    (b) Improved exercise tolerance
    (c) Decreased hospitalizations (28% relative risk reduction compared with placebo)
    (d) No effect on mortality
    (e) Notable clinical trial: DIG
  iii. Mechanism of action (in HF)
    (a) Inhibits myocardial Na-K adenosine triphosphatase
    (b) Decreases central sympathetic outflow by sensitizing cardiac baroreceptors
    (c) Decreases renal reabsorption of Na
    (d) Minimal increase in cardiac contractility
  iv. Dosing and administration considerations
    (a) For most patients, 0.125 mg/day is adequate to achieve the desired serum concentration.
    (b) Consider dosing 0.125 mg every other day in patients older than 70 years, those with impaired renal function, or those with low lean body mass.
    (c) No indication to load patients with digoxin in the setting of HF
    (d) Avoid abrupt discontinuation; can precipitate clinical deterioration
    (e) Drug interactions: Digoxin concentrations are increased with concomitant:
      (1) Clarithromycin, erythromycin
      (2) Amiodarone (reduce digoxin dose by 30%–50% or reduce dosing frequency)
      (3) Dronedarone (reduce digoxin dose by 50%)
      (4) Itraconazole, posaconazole
      (5) Cyclosporine, tacrolimus
      (6) Verapamil
  v. Monitoring
    (a) Serum concentrations should be less than 1 ng/mL; in general, concentrations of 0.5–0.9 ng/mL are suggested.
      (1) Minimizes the risk of adverse effects and ventricular arrhythmias associated with increased concentrations.
      (2) Risk of toxicity increases with age and renal impairment.
      (3) Risk of toxicity increases in the presence of hypokalemia, hypomagnesemia, or hypercalcemia.
      (4) Signs of toxicity generally include nausea, vomiting, vision changes.
    (b) SCr should be monitored because the drug is primarily cleared renally.

g. Hydralazine/isosorbide dinitrate
   i. Place in therapy
      (a) Recommended in addition to ACE inhibitors and β-blockers to reduce morbidity and mortality for patients self-described as African American with NYHA class III or IV HF*r*EF (class I indication)
      (b) May be useful in patients with current or prior symptoms of HF*r*EF who are unable to tolerate an ACE inhibitor or an ARB (class IIa indication)
   ii. Benefits
      (a) Decreased mortality (43% relative risk reduction compared with placebo in African American patients)
      (b) Reduced pulmonary congestion and improved exercise tolerance
      (c) Notable clinical trials: V-HeFT and A-HeFT
   iii. Mechanism of action
      (a) Hydralazine
         (1) Arterial vasodilator (reduces afterload)
         (2) Increases effect of nitrates through antioxidant mechanisms
      (b) Isosorbide dinitrate
         (1) Stimulates nitric acid signaling in the endothelium
         (2) Venous vasodilator (reduces preload)
   iv. Dosing and administration considerations
      (a) Fixed-dose BiDil (hydralazine 37.5 mg plus isosorbide dinitrate 20 mg) starting at 1 tablet three times daily with a goal dose of 2 tablets three times daily
      (b) Hydralazine 75 to 300 mg daily in 3 or 4 divided doses; isosorbide dinitrate 60–120 mg daily in 3 or 4 divided doses
   v. Monitoring
      (a) Headache
      (b) Hypotension
      (c) Drug-induced lupus (with hydralazine)

h. Sacubitril/valsartan
   i. Place in therapy
      (a) Novel therapy approved by the U.S. Food and Drug Administration (FDA) in 2015
      (b) According to the 2017 ACC/AHA/Heart Failure Society of America Focused Update of the HF guidelines
         (1) The clinical strategy of inhibition of the renin-angiotensin-aldosterone system with ACE inhibitors (level of evidence: A) OR ARBs (level of evidence: A), OR sacubitril/valsartan (level of evidence: B) in conjunction with evidence-based β-blockers and ARAs is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality (class I recommendation)
         (2) In patients with chronic symptomatic NYHA class II or III HF*r*EF who can tolerate an ACE inhibitor or ARB, replacement by sacubitril/valsartan is recommended to further reduce morbidity and mortality (class I recommendation).
   ii. Benefits
      (a) Decreased composite endpoint of death from CV causes or hospitalization for HF (20% relative risk reduction compared with enalapril monotherapy)
      (b) Decreased all-cause mortality (16% relative risk reduction) and CV death (20% relative risk reduction) compared with enalapril monotherapy
      (c) Decreased hospitalization for HF (21% relative risk reduction compared with enalapril monotherapy)
      (d) Notable clinical trial: PARADIGM-HF

iii. Mechanism of action
  (a) Sacubitril—prodrug metabolized to an active metabolite that inhibits neprilysin, increasing levels of natriuretic peptides
  (b) Valsartan—ARB, selectively blocks the angiotensin I receptor and inhibits angiotensin II–dependent aldosterone release
iv. Dosing and administration considerations
  (a) Initial dose
    (1) Not currently taking ACE inhibitor or ARB, switching from low dose ACE inhibitor (e.g., total daily dose of enalapril ≤10 mg, lisinopril ≤ 10 mg, ramipril ≤5 mg, or equivalent) or ARB (e.g., total daily dose of valsartan ≤160 mg, losartan ≤50 mg, olmesartan ≤10 mg, or equivalent), or eGFR <30 mL/min/m^2: sacubitril 24 mg/valsartan 26 mg twice daily
    (2) Switching from a standard dose ACE inhibitor (e.g., total daily dose of enalapril >10 mg, lisinopril >10 mg, ramipril >5 mg, or equivalent) or ARB (e.g., total daily dose of valsartan >160 mg, losartan >50 mg, olmesartan >10 mg, or equivalent): sacubitril 49 mg/valsartan 51 mg twice daily
  (b) Maintenance dose: Double the dose every 2–4 weeks to a target dose of sacubitril 97 mg/valsartan 103 mg twice daily, as tolerated.
  (c) If switching from an ACE inhibitor, allow a 36-hour washout period before initiating sacubitril/valsartan.
  (d) Because sacubitril is a neprilysin inhibitor, BNP will increase with use. However, NT-proBNP levels will not change.
v. Monitoring
  (a) Observe for signs and symptoms of angioedema and hypotension.
  (b) Monitor renal function and K 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients (e.g., preexisting hypotension, DM, K supplements, azotemia).
  (c) Monitor fluid status because patients may require a dose reduction in diuretic therapy.

i. Ivabradine
  i. Place in therapy
    (a) Novel therapy approved by the FDA in 2015
    (b) According to the 2017 ACC/AHA/Heart Failure Society of America Focused Update of the HF guidelines, ivabradine can be beneficial to reduce HF hospitalizations for patients with symptomatic (NYHA class II and III), stable, chronic HF*r*EF (LVEF of 35% or less) who are receiving evidence-based therapies, including a β-blocker at maximum tolerated dose, and who are in sinus rhythm (SR) with an HR of 70 beats/minute or greater at rest (class IIa recommendation).
  ii. Benefits
    (a) Decreased composite endpoint of CV death or hospitalization for HF (18% relative risk reduction compared with placebo)
    (b) Decreased hospitalization for HF (26% relative risk reduction compared with placebo)
    (c) Notable clinical trial: SHIFT
  iii. Mechanism of action: Selectively inhibits the I_f current in the sinoatrial node, providing HR reduction
  iv. Dosing and administration considerations
    (a) Given the well-proven mortality benefits of β-blocker therapy, patients should be receiving β-blockers at maximally tolerated or target doses or have a contraindication to β-blocker therapy before assessing the resting HR for consideration of ivabradine initiation.
    (b) Initial dosing: 5 mg twice daily

(c) After 2 weeks, adjust dose according to HR:
(1) Resting HR greater than 60 beats/minute: Increase dose by 2.5 mg twice daily.
(2) Resting HR 50–60 beats/minute: Continue current dose.
(3) Resting HR less than 50 beats/minute or signs/symptoms of bradycardia: Decrease dose by 2.5 mg twice daily.
(d) Maximum dose: 7.5 mg twice daily
(e) Contraindications: ADHF, BP <90/50 mm Hg, resting HR <60 beats/min, sinoatrial block, concomitant use with strong CYP3A4 inhibitors

v. Monitoring
(a) Assess HR and rhythm for bradycardia (6%–10%) and AF (5%–8%) after 2 weeks of therapy initiation or modification and periodically thereafter
(b) Phosphenes (3%): transient rings or spots of light in the visual field

j. Other medication therapies
i. Anticoagulation
(a) Recommended for HF with permanent, persistent, or paroxysmal AF with an additional risk factor for stroke (no preference on agent)
(b) Reasonable for patients with HF who have permanent, persistent, or paroxysmal AF without an additional risk factor for stroke
(c) Not recommended in the absence of AF, prior stroke, or a cardioembolic source
ii. Statins: Not recommended solely on the basis of HF diagnosis
iii. Antiarrhythmics: Given the neutral effects on mortality, the preferred antiarrhythmics in patients with HF*r*EF are dofetilide (AF/atrial flutter) and amiodarone.
iv. Nondihydropyridine (DHP) calcium channel blockers (CCBs) with negative inotropic effects can be harmful in patients with a low EF and should be avoided (class III recommendation: harm).
v. DHP CCBs: DHP CCBs have no proven benefit on morbidity or mortality in HF. Use of amlodipine can be considered for HTN or ischemic heart disease management in HF patients because of its neutral effects on morbidity and mortality.
vi. Dapagliflozin: May be used as an add-on therapy in persistently symptomatic HFrEF with elevated N-terminal pro-brain natriuretic peptide levels in eligible patients with or without diabetes

k. Device therapy
i. Implantable cardioverter defibrillator recommended for primary prevention of sudden cardiac death in the following patients with ischemic or nonischemic HF*r*EF:
(a) Patients with ischemic or nonischemic HFrEF (LVEF of 35% of less) and NYHA class II or III symptoms on chronic optimal medical therapy. Life expectancy should be greater than 1 year, and patient must be at least 40 days post-MI (class I indication).
(b) Patients with HF*r*EF (LVEF of 30% or less) resulting from previous MI and NYHA class I symptoms on chronic optimal medical therapy. Life expectancy should be greater than 1 year, and patient should be at least 40 days post-MI (class I indication).

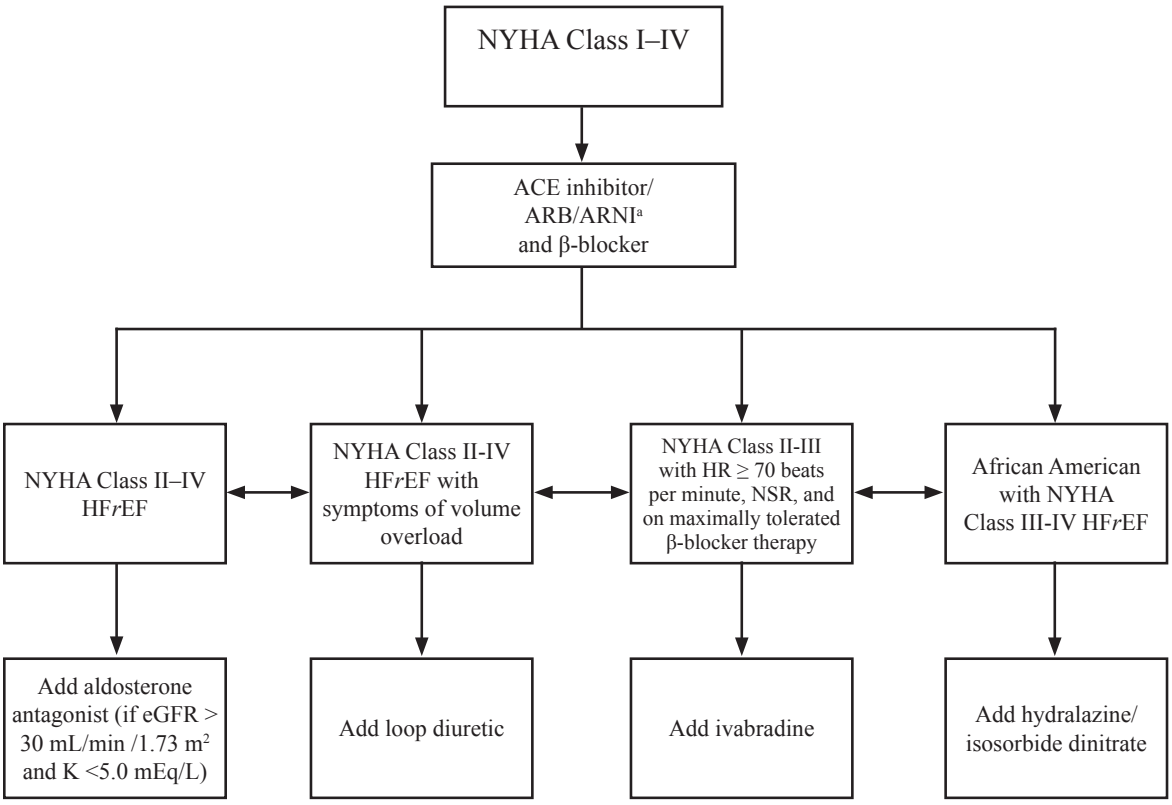

NYHA Class I–IV
ACE inhibitor/ ARB/ARNI[a] and β-blocker
NYHA Class II–IV HFrEF
NYHA Class II-IV HFrEF with symptoms of volume overload
NYHA Class II-III with HR ≥ 70 beats per minute, NSR, and on maximally tolerated β-blocker therapy
African American with NYHA Class III-IV HFrEF
Add aldosterone antagonist (if eGFR > 30 mL/min /1.73 m2 and K <5.0 mEq/L)
Add loop diuretic
Add ivabradine
Add hydralazine/ isosorbide dinitrate

Figure 1. Algorithm for pharmacologic management of heart failure with reduced ejection fraction.

[a]In PARADIGM-HF, patients were stabilized on an ACE inhibitor prior to conversion to sacubitril/valsartan

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; CrCl = creatinine clearance; K = potassium; NSR = normal sinus rhythm; NYHA = New York Heart Association.

Adapted from: Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137-61.

ii. Chronic resynchronization therapy recommended for those with an LVEF of 35% or less, in SR, and a left bundle branch block with a QRS of 150 milliseconds or greater on optimal medical therapy with NYHA class II–III symptoms or NYHA class IV with ambulation

2. Nonpharmacologic therapy
   a. Prevent further cardiac injury.
      i. Discontinue smoking.
      ii. Reduce weight if obese.
      iii. Control HTN (goal BP < 130/80 mm Hg per the 2017 ACC/AHA/Heart Failure Society of America Focused Update of the HF guidelines)
      iv. Control DM.
      v. Decrease alcohol intake to 2 or fewer drinks per day for men and 1 or fewer drinks per day for women. Eliminate alcohol intake if cardiomyopathy is alcohol induced.
      vi. Limit Na intake to 1500 mg/day for stages A and B; consider less than 3 g/day for stages C and D.
      vii. Treat sleep apnea.
      viii. Educate patient about appropriate self-care.

b. Restricting fluid intake to 1.5–2 L/day is reasonable in stage D if serum Na is low.
c. Modest exercise program benefits
    i. Possible modest effects on all-cause hospitalization and all-cause mortality, CV death or CV hospitalization, and CV death or HF hospitalization
    ii. Safe for patients with HF
d. Influenza and pneumococcal vaccines
e. Monitor and appropriately replace electrolytes (to minimize risk of arrhythmias).
f. Monitor for thyroid disease.
    i. Hypothyroidism can be masked by HF symptoms.
    ii. Hyperthyroidism will worsen systolic dysfunction.
g. Screen for and treat depression.

Patient Case

3. Which drug that J.T. (from Patient Case 2) is currently taking would be best to discontinue because of his HF*r*EF?

    A. Acetaminophen.

    B. Sertraline.

    C. Cilostazol.

    D. Levothyroxine.

C. HF*p*EF: Clinical evidence for efficacious agents for HF*p*EF has generally been disappointing. Therapies for symptoms, comorbidities, and risk factors that can worsen CV disease are recommended.
    1. Class I recommendations
        a. SBP and diastolic blood pressure (DBP) should be well controlled. HTN impairs myocardial relaxation and promotes cardiac hypertrophy. Goal SBP less than 130 mm Hg per the 2017 ACC/AHA/HFSA Focused Update of the HF guidelines
        b. Diuretics should be used for symptom relief in volume overload.
    2. Class IIa recommendations
        a. Coronary revascularization is reasonable in patients with CHD who have angina or demonstrable myocardial ischemia that is judged to be symptomatic despite optimal therapy.
        b. Management of AF is reasonable to improve symptomatic HF.
        c. The use of β-blockers, ACE inhibitors, and ARBs in patients with HTN is reasonable to control BP.
    3. Class IIb recommendation: Use of ARAs might be considered to decrease hospitalizations in patients with HF*r*EF already on ACE inhibitors/ARBs and β-blockers.
    4. Other recommendations
        a. Control tachycardia.
            i. Tachycardia decreases the time for the ventricles and coronary arteries to fill with blood.
            ii. Control of HR improves symptoms of HF.
            iii. Can use β-blockers or non-DHP CCBs
            iv. DHP CCBs may cause reflex tachycardia, potentiating diastolic dysfunction.
        b. Symptoms of breathlessness can be relieved using nitrates in addition to diuretics. Avoid use of nitrates in HFpEF without concomitant symptomatic coronary artery disease.

D. HFrecEF: HF with recovered LVEF is defined as a documented LVEF of less than 40% at baseline plus a documented LVEF improvement of 10% or greater and a second LVEF measurement of greater than 40%.
   1. HFrecEF is distinct from both HFrEF and HFpEF because of distinct biology and improved outcomes compared with the other two causes.
   2. Guideline-directed medical therapy (e.g., ACE inhibitors, ARBs, ß-blockers) should not be discontinued in HFrecEF; discontinuation may cause HF recurrence.
   3. Cessation of diuretic regimens is encouraged, when tolerable.
   4. Patients who cannot tolerate diuretic discontinuation should be considered for further titration of guideline-directed medical therapy to target doses, and for conversion of ACE inhibitors or ARBs to an angiotensin receptor-neprilysin inhibitor (ARNI)
   5. Patients with HFrecEF should be evaluated in the clinic every 6–12 months.

E. Medications That Cause/Exacerbate HF: An AHA scientific statement addresses medications that can cause or exacerbate HF. Drugs to avoid or use with caution in HF include:
   1. Drugs that promote sodium and water retention
      a. Nonsteroidal anti-inflammatory drugs (NSAIDs, including selective cyclooxygenase-2 inhibitors)
         i. Promote Na and water retention
         ii. Blunt diuretic response
         iii. Increase morbidity and mortality
      b. Corticosteroids
      c. Minoxidil
      d. Thiazolidinediones
   2. Drugs with negative inotropic effects
      a. Class I and III antiarrhythmic agents (except for amiodarone and dofetilide)
         i. Also have proarrhythmic effects
         ii. Amiodarone and dofetilide are safe in patients with HF.
         iii. Avoid dronedarone; it is contraindicated in patients with symptomatic HF with recent decompensation necessitating hospitalization or NYHA class IV HF.
      b. CCBs (except for amlodipine and felodipine)
         i. Also promote neurohormonal activation
         ii. Amlodipine and felodipine have been proven safe in patients with HF and can be added when additional BP reduction is needed; monitor for edema.
      c. Cilostazol
      d. Itraconazole
   3. Other
      a. Metformin: Increased risk of lactic acidosis (black box warning)
      b. Amphetamines (e.g., methylphenidate)
         i. α- and β-agonist activity
         ii. Cause tachycardia
         iii. Proarrhythmic effects
      c. Pregabalin
         i. Inhibits calcium channels
         ii. Lower-extremity edema, HF exacerbation
      d. Nutritional supplements
         i. Lack of evidence
         ii. Lack of product regulation
         iii. Potential for drug interactions and/or increased risk of bleeding

II. ATRIAL FIBRILLATION

A. Background
   1. Prevalence
      a. Most common arrhythmia: 2.2 million Americans
      b. Prevalence increases with age.
      c. Common comorbidity in patients with valvular heart disease or HF
   2. Symptoms
      a. Some patients have no symptoms.
      b. Potential symptoms that may be present to some degree include the following:
         i. Palpitations
         ii. Chest pain
         iii. Dyspnea
         iv. Fatigue
         v. Lightheadedness
      c. Rare cases of thromboembolic events
      d. Symptoms vary with ventricular rate, underlying LVEF, AF duration, and individual patient perceptions.
   3. Classification
      a. Paroxysmal: Spontaneous self-termination within 7 days of onset
      b. Persistent: Lasting more than 7 days
      c. Long-standing persistent: Continuous duration of more than 12 months
      d. Permanent: Present all the time, unable to return to SR using pharmacologic or nonpharmacologic options
      e. Nonvalvular: The absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair

Patient Case

4. P.M. is a 52-year-old man (height 70 inches, weight 116 kg) with a history of HTN and a transient ischemic attack 2 years ago. He visits his primary care doctor with the chief concern of several weeks of a "fluttering" feeling in his chest on occasion. He thinks the fluttering is nothing; however, his wife insists he have it checked. His current medications include metoprolol tartrate 50 mg twice daily and aspirin 81 mg/day. He is adherent to this regimen and has health insurance, but he does not like to make the 3-hour trip to his primary care provider. His laboratory data from his past visit were all within normal limits. His vital signs today include BP 130/78 mm Hg and HR 76 beats/minute. All laboratory values are within normal limits. An electrocardiogram (ECG) reveals an irregularly irregular rhythm, with no P waves, and a HR of 74 beats/minute. A diagnosis of AF is made. What is the best approach for managing his AF at this time?

   A. Begin digoxin 0.25 mg/day.

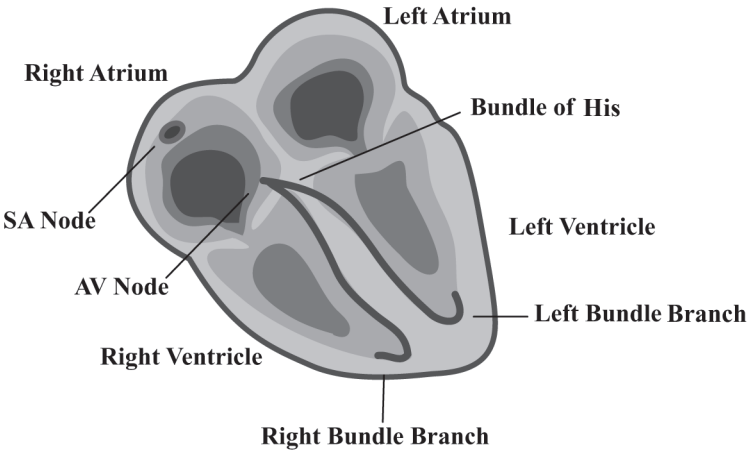
   B. Begin diltiazem CD 240 mg/day.

   C. Begin warfarin 5 mg/day and titrate to a goal INR of 2.5.

   D. Begin dabigatran 150 mg twice daily.

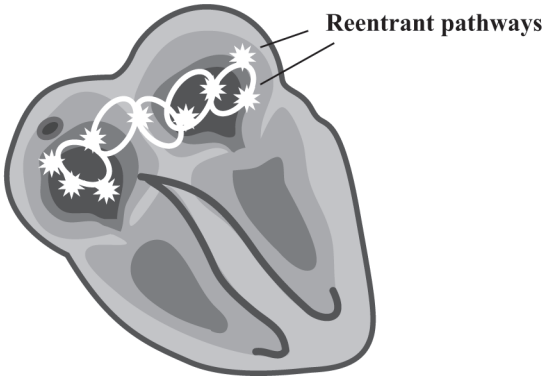
B. Pathophysiology

1. Cardiac conduction in a normal heart and a heart with atrial fibrillation (Figure 2)



The impulse:
1. Is generated by the SA node.
2. Propagates through atrial tissue.
3. Reaches the AV node.
4. Passes slowly through the AV node.
5. Travels through the bundle of His.
6. Is conducted simultaneously down the three bundle branches.
7. Is distributed to the ventricular tissue by small embedded Purkinje fibers.

Figure 2. Cardiac conduction and atrial fibrillation.



The impulses:
1. Are generated in atrial tissues; ± focal activation, with reentry pathways
2. Bombard the AV node in a rapid and chaotic fashion.
3. Are propagated by the AV node after it repolarizes from the last impulse.
4. See 5–7 above.

Figure 2. Cardiac conduction and atrial fibrillation. *(continued)*
AV = atrioventricular; SA = sinoatrial.

2. ECG findings

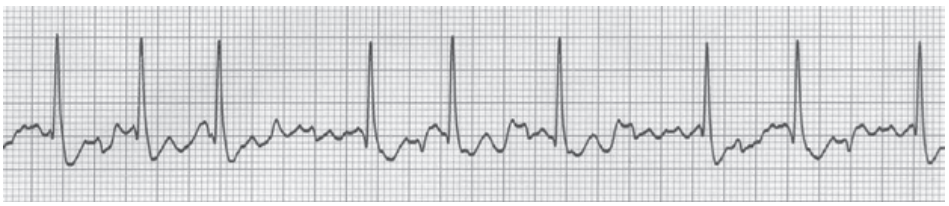


Figure 3. Electrocardiogram showing atrial fibrillation.

3. AF causes (Table 7).

Table 7. Potential Causes of AF

Atrial Distension	High Adrenergic Tone
Chronic hypertension	Alcohol withdrawal
Mitral valve disease	Thyrotoxicosis
Cardiomyopathy	Sepsis
Congenital defects	Binge drinking
Pulmonary hypertension	Surgery
Acute pulmonary embolus	Sympathomimetics such as cocaine or amphetamines
Myocardial ischemia	Excessive theophylline, caffeine
Sleep apnea	
Emphysema or other lung diseases	

C. Pharmacologic therapy
   1. Ventricular rate control
      a. If patients have a rapid ventricular rate, AV nodal blockade is necessary.
      b. Goal HR (resting HR less than 80 beats/minute) is reasonable in symptomatic patients (class IIa recommendation). A more lenient rate control (resting HR less than 110 beats/minute) may be reasonable in patients who are asymptomatic and have preserved ejection fraction (class IIb recommendation).
      c. The goal is to reduce symptoms and possibly prevent tachycardia-induced cardiomyopathy.
      d. Select the best agent according to individual clinical response and concomitant disease states.
         i. β-Blockers
            (a) Any agent with β-blockade can be used and dosed to the goal HR.
            (b) Labetalol or carvedilol if additional α_1-blockade is desirable (e.g., HTN)
            (c) Effective for controlling exercise-associated HR increases
            (d) β-Blockers may be preferred in patients with a history of MI.
            (e) Select carvedilol, metoprolol succinate, or bisoprolol in patients with HF*r*EF
            (f) Avoid in patients with Wolff-Parkinson-White syndrome.
         ii. Non-DHP CCBs: Verapamil or diltiazem
            (a) Avoid use if there is concomitant systolic dysfunction.
            (b) May be preferred over β-blocker in patients with asthma or severe chronic obstructive pulmonary disease
            (c) Effective for controlling exercise-associated HR increases
            (d) Avoid in patients with Wolff-Parkinson-White syndrome.
         iii. Digoxin
            (a) Often ineffective alone for controlling ventricular rate in AF, especially during exercise or movement (because of minimal effectiveness with sympathetic stimulation)
            (b) Can be included in regimen if patient has HF*r*EF
            (c) May be effective if additional HR control is needed when a patient is already receiving a β-blocker, diltiazem, or verapamil
            (d) Avoid in patients with Wolff-Parkinson-White syndrome.
            (e) May be agent of choice if patient has uncontrolled HR and decompensated HF
         iv. Amiodarone
            (a) May be used for rate control in patients with HF who do not have an accessory pathway
            (b) May be used for rate control in patients who are refractory to other therapies such as β-blockers, non-DHP CCBs, and digoxin

2. Rhythm control: Maintaining SR offers no advantage over controlling the ventricular rate (AFFIRM trial). However, in specific patients with intractable and intolerable symptoms (dyspnea, palpitations, and exercise intolerance) despite adequate rate control or in patients for whom adequate ventricular rate control cannot be achieved, restoration and maintenance of SR may be desirable (Table 8).

Table 8. Summary of the Pros and Cons of Rate Control vs. Rhythm Control

	Pros	Cons
Rate control strategy	Generally easy to achieve and maintain; out-of-hospital therapy typical	Electrical and structural remodeling because of continued AF makes future attainment of SR virtually impossible; safety not proven for younger patients
Rhythm control strategy	If patient is symptomatic with fatigue and exercise intolerance, these symptoms may improve if SR is attained (especially in patients with HF); minimizes development of structural atrial changes; acceptable for all age groups	Adverse effects of antiarrhythmic medications; cost of medications and monitoring; likelihood of AF recurrence; in-hospital stay may be necessary to initiate therapy

AF = atrial fibrillation; HF = heart failure; SR = sinus rhythm.

a. Cardioversion in AF
    i. If cardioversion is attempted (electric or pharmacologic), the absence of atrial thrombi must be ensured.
    ii. Without anticoagulation (thrombi caused by decreased or stagnant blood flow in the atria)
        (a) AF for more than 48 hours = 15% rate of atrial thrombus.
        (b) AF for more than 72 hours = 30% rate of atrial thrombus.
    iii. Thrombi present plus cardioversion = 91% stroke rate.
    iv. Ensure safe cardioversion by either:
        (a) Transesophageal echocardiogram (TEE) to visualize the atria, *or*
        (b) Three or more weeks of therapeutic anticoagulation
            (1) INR 2.0-3.0 if warfarin is selected
            (2) DOACs may also be used
    v. Continue anticoagulation for at least four weeks after cardioversion with either:
        (a) Warfarin or
        (b) A DOAC

vi. Specific recommendations for anticoagulation are described in Table 9.

Table 9. Anticoagulation Strategies Surrounding Cardioversion of AF[a]

AF Type	Anticoagulation Recommendations
Unstable AF	• Synchronized cardioversion; anticoagulate immediately beforehand with parenteral therapy • Anticoagulate for ≥4 wk after cardioversion with warfarin or a DOAC if AF ≥ 48 hr or if duration is unknown
Stable AF, duration <48 hr[b]	ACCP (CHEST) guidelines: • Anticoagulate at presentation and continue through cardioversion – LMWH or UFH at full treatment doses • Anticoagulate for ≥4 wk afterward, regardless of baseline risk of stroke ACC/AHA/HRS AF guidelines: • Anticoagulation as soon as possible before cardioversion is recommended with a CHA_2DS_2-VASc score of ≥2 (men) or ≥3 (women); anticoagulation may be considered with a score of 0-1 (men) or 1-2 (women) – UFH, LMWH, or DOAC • Need for anticoagulation after cardioversion should be based on the patient's risk of thromboembolism, according to their CHA_2DS_2-VASc score
Stable AF, duration unknown or >48 hr (no TEE)	ACCP (CHEST) guidelines: • Anticoagulate for 3 wk before cardioversion – Warfarin with INR 2.0–3.0 or a DOAC • Anticoagulate for ≥4 wk afterward, regardless of baseline risk of stroke ACC/AHA/HRS AF guidelines: • Anticoagulate for ≥3 wk before cardioversion – Warfarin with INR 2.0–3.0 2.0-3.0 or DOAC, dabigatran, rivaroxaban, apixaban, or enoxaparin (full treatment doses) • Anticoagulate for 4 wk after cardioversion, regardless of CHA_2DS_2-VASc score
Stable AF, duration unknown or >48 hr (with TEE-guided cardioversion)	ACCP (CHEST) guidelines: • TEE-guided therapy with abbreviated anticoagulation before cardioversion – LMWH or UFH at full treatment doses should be initiated at the time of TEE, and cardioversion should be performed within 24 hr of TEE if no thrombus is seen • Anticoagulate for ≥4 wk after cardioversion, regardless of baseline risk of stroke ACC/AHA/HRS AF guidelines: • If no identifiable thrombus seen on TEE, cardioversion is reasonable, provided anticoagulation is achieved before TEE • If thrombus identified on TEE, 3 wk of therapeutic anticoagulation is required before cardioversion • Anticoagulation should be maintained after cardioversion for ≥4 wk

[a]Potential risk of cardioversion with antiarrhythmic drugs should be considered before treatment initiation.

[b]No randomized trials have compared different anticoagulation strategies in patients with AF < 48 hr.

ACC = American College of Cardiology; ACCP = American College of Chest Physicians; AF = atrial fibrillation; AHA = American Heart Association; DOAC = direct oral anticoagulant; HRS = Heart Rhythm Society; INR = international normalized ratio; LMWH = low-molecular-weight heparin; TEE = transesophageal echocardiography; UFH = unfractionated heparin.

Updated citation:
Lip GY, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest 2018 Aug 21. [Epub ahead of print]

b. Oral antiarrhythmic agents to induce or maintain SR (class Ic and class III agents are recommended in atrial fibrillation; choice of agent depends on patient comorbidities)
   i. Class Ic antiarrhythmics: 80% - 90% efficacy
      (a) Flecainide and propafenone can be considered first-line therapies for patients without structural heart disease (Figure 4). Propafenone also displays some nonselective β-blocking properties.
      (b) Concomitant AV nodal blocking agent (e.g., β-blocker or non-DHP CCB) typically required
      (c) Contraindicated in patients with structural heart disease (including CHD, HF, left ventricular hypertrophy, and valvular heart disease)
   ii. Class III antiarrhythmics
      (a) Amiodarone: 85%–95% efficacy
         (1) Has electrophysiologic properties of classes I–IV
         (2) Oral loading dose required (e.g., 400 mg 2 or 3 times per day for 2 weeks and then 400 mg/day for 4 weeks, followed by a 200-mg/day maintenance dose). Achieving a loading dose of 10 g is desirable. Many different regimens exist.
         (3) Long half-life of about 60 days
         (4) In addition, has AV nodal blocking properties, which may help to control HR if AF recurs
         (5) May use in patients with HF
         (6) Hepatically metabolized: Cytochrome P450 (CYP) 3A4 substrate; inhibitor of CYP3A4, CYP1A2, CYP2C9, CYP2D6, and P-glycoprotein (P-gp)
         (7) Minimal incidence of ventricular arrhythmias
         (8) Drug interactions (many)
            (A) Digoxin: Increased digoxin exposure. Lower digoxin dose by 50%.
            (B) Warfarin: Increased warfarin exposure. Lower warfarin dose by 33%–50%.
            (C) Simvastatin: Increased simvastatin exposure. Do not exceed dose of 20 mg/day.
            (D) Lovastatin: Increased lovastatin exposure. Do not exceed dose of 40 mg/day.
            (E) β-Blockers, non-DHP CCBs, clonidine, ivabradine: Additive bradycardia
         (9) Extensive monitoring for noncardiac adverse effects
            (A) Liver function tests (LFTs): Baseline and every 6 months
            (B) Thyroid function tests: Baseline and every 6 months
            (C) Chest radiography: Baseline and annually
            (D) ECG: Periodically
            (E) Pulmonary function tests (including D_LCO [carbon dioxide diffusion in the lungs]): Baseline and for unexplained cough/dyspnea, chest radiographic abnormalities or clinical suspicion. Discontinue if pulmonary fibrosis occurs.
            (F) Ophthalmologic examination: Baseline (if visual impairment) and if patient has symptoms of visual impairment. Discontinue if optic neuritis occurs.
            (G) Skin toxicities: "Blue skin" syndrome and sunburn
            (H) Neurologic toxicity: Tremor, neuropathy
            (I) Nausea, vomiting
            (J) Adverse effects may require increased monitoring, dose reduction, or drug discontinuation
      (b) Sotalol: 50%–60% efficacy
         (1) Renal excretion. Dose adjustment and vigilant corrected QT (QTc) interval monitoring necessary in renal impairment. Recommended starting dose is 80 mg twice daily (unless creatinine clearance [CrCl] less than 60 mL/minute, then once daily).
         (2) Should be initiated in the hospital (minimum of 3-day stay), where QTc interval, serum electrolytes (e.g., K and magnesium), and renal function can be monitored

(3) Contraindicated in patients with HF (stable or unstable); CrCl less than 40 mL/minute; QTc interval greater than 450 milliseconds; and second- or third-degree AV block or sick sinus syndrome (in absence of pacemaker)
(4) Possesses nonselective β-blocking properties; may result in additive bradycardia with β-blockers, non-DHP CCBs, clonidine, ivabradine, and digoxin

(c) Dofetilide: 50%–60% efficacy
(1) Should be initiated in the hospital (minimum of 3-day stay) so that QTc interval, serum electrolytes (e.g., K and magnesium), and renal function can be monitored
(2) Starting dose is selected based on renal function
(A) CrCl greater than 60 mL/minute: 500 mcg twice daily
(B) CrCl 40–60 mL/minute: 250 mcg twice daily
(C) CrCl 20–39 mL/minute: 125 mcg twice daily
(D) CrCl less than 20 mL/minute: Contraindicated
(3) Modification of subsequent doses is based on QTc interval measured 2–3 hours after initial dose: QTc > 500 milliseconds (or 550 milliseconds in ventricular conduction abnormalities) OR QTc increased greater than 15% above baseline: reduce dose by 50%
(4) If QTc is greater than 500 milliseconds (or 550 milliseconds in ventricular conduction abnormalities) at any point after in-hospital doses 2–5, discontinue dofetilide
(5) Hepatically metabolized by CYP3A4
(6) Renal elimination through renal cationic secretion; check QTc interval if renal function declines
(7) Contraindicated in patients with CrCl less than 20 mL/minute or QTc interval greater than 440 milliseconds (or 500 milliseconds for patients with ventricular conduction abnormalities)
(8) May use in patients with HF
(9) Drug interactions
(A) Avoid concomitant use of the following drugs: cimetidine, verapamil, itraconazole, ketoconazole, hydrochlorothiazide, prochlorperazine, megestrol, dolutegravir, and trimethoprim alone or in combination with sulfamethoxazole
(B) Use CYP3A4 inhibitors, triamterene, metformin, and amiloride with caution: increased dofetilide exposure

(d) Dronedarone: 21%–25% efficacy
(1) Amiodarone analog lacking the iodine moiety that contributes to the thyroid toxicity of amiodarone
(2) Has electrophysiologic properties of classes I–IV
(3) Dose: 400 mg twice daily with morning and evening meal
(4) Hepatically metabolized; CYP3A4 substrate; CYP3A4, CYP2D6, and P-gp inhibitor
(5) Half-life is 13–19 hours.
(6) Small increase in SCr by 0.1 mg/dL probably a result of inhibition of creatinine's tubular secretion; rapid onset, will plateau after 7 days, and is reversible. Monitor SCr periodically.
(7) Acute kidney injury has also been reported, and it is usually reversible with drug discontinuation.
(8) Contraindicated in permanent AF; NYHA class II or III HF with recent decompensation necessitating hospitalization; NYHA class IV HF; second- or third-degree AV block or sick sinus syndrome (in absence of pacemaker); severe liver impairment, HR less than 50 beats/minute; concurrent use of strong CYP3A4 inhibitors or QTc interval–prolonging agents; history of amiodarone-induced hepatotoxicity or pulmonary toxicity; pregnancy; or QTc interval 500 milliseconds or greater

(9) One trial found dronedarone less effective than amiodarone for the maintenance of SR, but with fewer adverse effects.
(10) Drug interactions
  (A) Digoxin: Increased digoxin exposure; lower digoxin dose by 50%
  (B) β-Blockers, non-DHP CCBs, and clonidine: Excessive bradycardia; initiate these drugs at lowest dose. Diltiazem and verapamil can increase dronedarone exposure; therefore, monitor ECG.
  (C) Statins: Increased statin exposure. Limit dose of simvastatin to 10 mg/day and lovastatin to 20 mg/day.
  (D) Dabigatran: In patients with moderate renal impairment (CrCl 30–50 mL/minute), dronedarone increases dabigatran exposure; decrease dabigatran dose to 75 mg twice daily.
  (E) Strong CYP3A4 inhibitors and inducers: Avoid.
  (F) Cyclosporine, tacrolimus, sirolimus: Increased exposure of these agents; monitor serum concentrations closely
(11) Other safety issues
  (A) Liver injury: According to postmarketing surveillance, dronedarone has been associated with rare but severe hepatic liver injury.
  (B) Pulmonary toxicity: In postmarketing surveillance, cases of interstitial lung disease, including pneumonitis and pulmonary fibrosis, have been reported. Patients should report any new signs of dyspnea or nonproductive cough.

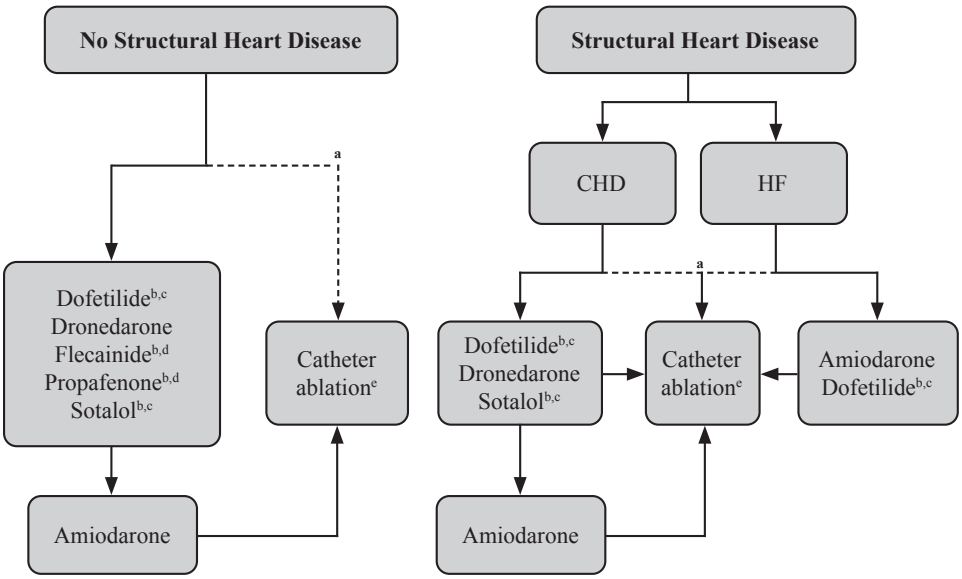


Figure 4. Options for rhythm control in patients with paroxysmal and persistent atrial fibrillation. Antiarrhythmics are listed in alphabetical order and not order of preference

[a]Depends on patient preference when performed in experienced centers.

[b]Not recommended with severe left ventricular hypertrophy (wall thickness > 1.5 cm).

[c]Use with caution in patients at risk of torsades de pointes ventricular tachycardia.

[d]Should be combined with atrioventricular nodal blocking agents.

[e]Catheter ablation is only recommended as first-line therapy for patients with paroxysmal atrial fibrillation (class IIa recommendation).

CHD = coronary heart disease; HF = heart failure.

Adapted with permission from: January CT, Wann SL, Sacco RL, et al. AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and Heart Rhythm Society. Circulation 2014;130:2071.

3. Antithrombotic therapy
    a. The average annual stroke rate is 5% per year without anticoagulation.
        i. A patient's individual risk can vary from about 1% to 20% per year depending on risk factors.
        ii. This risk is independent of current cardiac status (i.e., SR or AF).
    b. Risk stratification and treatment determination is based on the CHA_2DS_2-VASc score (Tables 10–11). Of note, the 2018 CHEST guidelines for anticoagulation in atrial fibrillation no longer recommend antiplatelet therapy alone for prevention of stroke or systemic embolism.

Table 10. Risk Stratification for Antithrombotic Therapy Using the CHA_2DS_2-VASc Score[a]

Risk Factor	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75 yr	2
Diabetes	1
Stroke, TIA, thromboembolism	2
Vascular disease	1
Age 65–74 yr	1
Sex category (female)	1

[a]For use in patients with nonvalvular atrial fibrillation. Maximum point value is 9.

CHF = congestive heart failure; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

Table 11. AHA/ACC/Heart Rhythm Society Guideline Recommendations for Antithrombotic Therapy in Patients with NVAF Based on CHA_2DS_2-VASc Score[a]

CHA_2DS_2-VASc Score of 0 in men or 1 in women	CHA_2DS_2-VASc Score of 1 in men or 2 in women	CHA_2DS_2-VASc Score of 2 in men or 3 in women
Reasonable to omit antithrombotic therapy or consider aspirin	Consider no antithrombotic therapy, oral anticoagulation, or aspirin	Oral anticoagulant therapy is indicated. DOAC over warfarin in DOAC-eligible patients

[a]AHA/ACC/Heart Rhythm Society guidelines

DOAC = direct oral anticoagulant.

Patient Case

5. H.D. is a 67-year-old man with a history of HTN, moderate mitral valve insufficiency, and AF for 4 years. His medications include ramipril 5 mg twice daily, sotalol 120 mg twice daily, digoxin 0.125 mg/day, and warfarin 5 mg/day. He visits his primary care physician today after being discharged from the emergency department with increased fatigue on exertion, palpitations, and lower extremity edema. His vital signs today include BP 115/70 mm Hg and HR 88 beats/minute, and all laboratory results are within normal limits; however, his lower extremity edema has worsened. His INR is 2.8. His ECG shows AF. An echocardiogram reveals an LVEF of 35%–40%. H.D.'s physician would like to continue a rhythm control approach. What is the best treatment option for managing his AF?

    A. Discontinue sotalol and begin metoprolol succinate 12.5 mg/day.

    B. Discontinue sotalol and begin dronedarone 400 mg twice daily.

    C. Discontinue sotalol and begin amiodarone 400 mg twice daily, tapering to goal dose of 200 mg/day for the next 6 weeks.

    D. Continue sotalol and add metoprolol tartrate 25 mg twice daily.

D. Nonpharmacologic therapies (procedures)
   1. Electrical cardioversion (low-energy cardioversion; sedation highly desirable)
   2. AV nodal ablation: Ablate AV node and chronically pace the ventricles.
   3. Pulmonary vein ablation: Ablates the origin of the abnormal atrial foci, which is often near the pulmonary vein–atrial tissue intersection.

III. HYPERTENSION

Definition: HTN is a persistent, nonphysiologic elevation of BP; it is defined as an SBP of 130 mm Hg or greater and/or a DBP of 80 mm Hg or greater.

A. Background
   1. Prevalence
      a. Most common chronic disease in the United States
      b. Affects 46% of the population
      c. Prevalence increases with age
      d. Major modifiable risk factor for CV disease and stroke
   2. Etiology
      a. Essential HTN: 90% (no identifiable cause)
         i. Obesity is a contributor
         ii. Evaluate Na intake
      b. Secondary HTN
         i. Primary aldosteronism
         ii. Renal parenchymal disease
         iii. Renal artery stenosis
         iv. Obstructive sleep apnea
         v. Cushing syndrome
         vi. Thyroid or parathyroid disease
         vii. Medications (e.g., cyclosporine, NSAIDs, sympathomimetics)
         viii. Pheochromocytoma
   3. Diagnosis
      a. Periodic screening for all people older than 21 years
      b. Patient should be seated quietly in chair for at least 5 minutes.
      c. Use appropriate cuff size (bladder length at least 80% the circumference of the arm).
      d. Take BP at least twice, separated by at least 2 minutes.
      e. The average BP on two separate visits is required to diagnose HTN accurately.
      f. Home blood pressure monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM) are recommended to confirm diagnosis, screen for white-coat HTN, and screen for masked HTN
         i. White-coat HTN: Office blood pressure is 130/80-160/100 mm Hg after a 3-month trial of lifestyle modification but with daytime ABPM or HBPM blood pressure less than 130/80 mm Hg
         ii. Masked HTN: Office blood pressure is 120-129/less than 80 mm Hg after a 3-month trial of lifestyle modification; daytime ABPM or HBPM blood pressure of 130/80 or greater
   4. Benefits of treating elevated BP
      a. Decreased risk of stroke (by 35-40%)
      b. Decreased risk of MI (by 20-25%)
      c. Decreased risk of HF (by 50%)

5. Effects of lifestyle modifications on BP (Table 12)

Table 12. Recommended Lifestyle Modifications

Modification	Recommendation	Approximate SBP Reduction
Weight reduction	Maintain a normal body weight (BMI 18.5–24.9 kg/m^2)	5–20 mm Hg per 10-kg weight loss
Adopt DASH eating plan (includes substantial K intake)	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg
Reduce Na intake	Reduce Na intake to < 1500 mg/day Reducing Na intake by at least 1000 mg/day will lower BP if desired daily Na intake goal is not achieved	2–8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min/day most days of the week)	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to: Men: 2 drinks/day (24 oz of beer, 10 oz of wine, or 3 oz of 80-proof whiskey) Women and those of lower body weight: 1 drink/day	2–4 mm Hg

BMI = body mass index; BP = blood pressure; DASH = Dietary Approaches to Stop Hypertension; Na = sodium; SBP = systolic blood pressure.

B. Therapeutic management
   1. Patient classification and management in adults (Table 13)

Table 13. Classification of BP and Hypertension and Lifestyle Modification Recommendations

BP Classification	SBP (mm Hg)		DBP (mm Hg)
Normal	< 120	*and*	< 80
Elevated	120-129	*and*	< 80
Stage 1 hypertension	130-139	*or*	80-89
Stage 2 hypertension	≥140	*or*	≥ 90
Hypertensive urgency/ emergency	>180	*or*	>120

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure

Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127-248.

Patient Cases

6. W.D. is a 55-year-old white female who was recently admitted to the hospital with acute myocardial infarction which was treated with a stent. She has a past medical history of HTN and GERD. She is visiting your clinic today for management of her cardiovascular medications. Her vitals today include BP 152/86 mm Hg and HR 82 beats/minute. Her labs are all WNL, including Na 140 mEq/L, K 4.3 mEq/L, and SCr 1.0 mg/dL. Her current medication regimen includes clopidogrel 75 mg daily, aspirin 81 mg daily, and atorvastatin 40 mg daily. What is the most appropriate approach to manage her HTN?
   A. Add carvedilol monotherapy
   B. Add lisinopril and metoprolol
   C. Add amlodipine and metoprolol
   D. Add lisinopril monotherapy

7. T.J. is a 45-year-old African American woman presenting for routine follow-up of her chronic obstructive pulmonary disease. She has no other medical history. Her blood pressure today (average of 2 readings) is 138/88 mm Hg. Her HR is 77 beats/minute. Her BP at her last visit was 136/85 mm Hg. Her current medications include tiotropium dry powder inhaler daily and an albuterol metered dose inhaler as needed. Her labs include Na 140 mEq/L, K 4.0 mEq/L, Cl 102 mEq/L, bicarbonate 28 mEq/L, blood urea nitrogen 14 mg/dL, and SCr 0.8 mg/dL. What is the best approach for managing her HTN?
   A. Begin diet and lifestyle modifications only
   B. Begin lifestyle modifications and add amlodipine 5 mg daily
   C. Begin lifestyle modifications and add lisinopril 2.5 mg daily
   D. Begin lifestyle modifications and add lisinopril 2.5 mg daily plus hydrochlorothiazide 12.5 mg daily

2. The 2017 11/AHA HTN guideline blood pressure thresholds and goals are listed in Table 14.

Table 14. BP Thresholds for Goals of Pharmacologic Therapy in Patients with HTN According to Clinical Condition

Clinical Condition	BP Threshold, mm Hg	BP Goal, mm Hg
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80 for all
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	
Diabetes mellitus[a]	≥130/80	
Chronic kidney disease	≥130/80	
Chronic kidney disease after renal transplantation	≥130/80	
Heart failure	≥130/80	
Stable ischemic heart disease	≥130/80	
Secondary stroke prevention	≥140/90	
Secondary stroke prevention (lacunar)	≥130/80	
Peripheral arterial disease	≥130/80	
Older persons (≥65 years; noninstitutionalized, ambulatory, community-living)	≥130 (SBP)	<130 (SBP)

[a]According to the 2017 ACC/AHA HTN guideline; 2018 ADA guideline does not agree.

ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CVD = cardiovascular disease; SBP = systolic blood pressure.

3. Blood pressure treatment strategies according to BP and ASCVD risk are located in Figure 5.

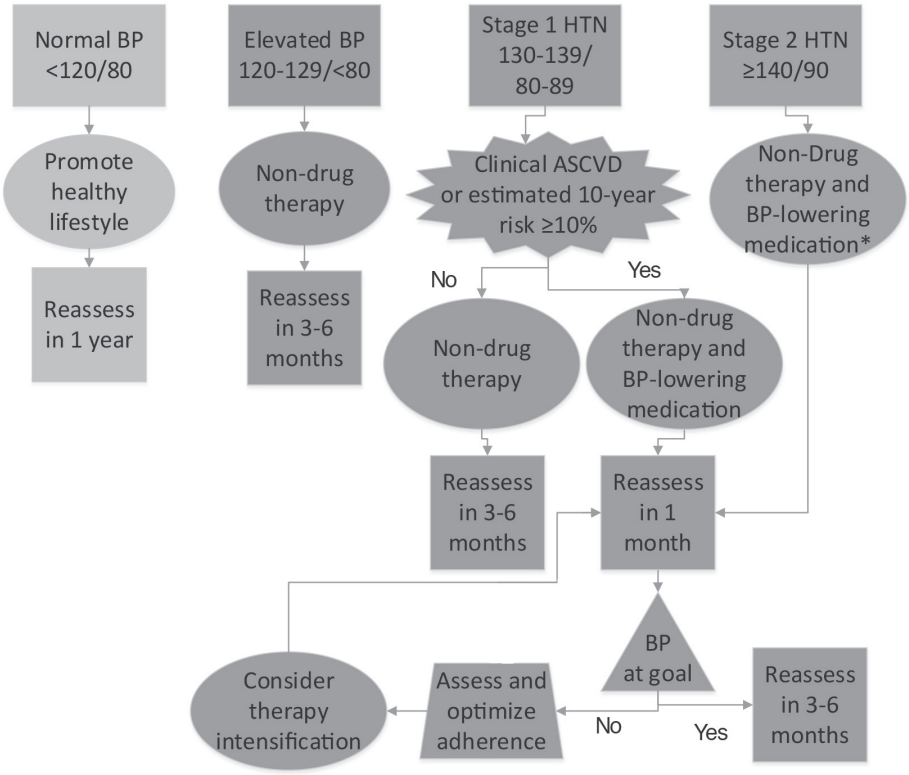


Figure 5. BP treatment strategies according to BP level and ASCVD risk.

*Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 HTN and an average blood pressure of greater than 20/10 mm Hg above their blood pressure target.

ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure.

Adapted from: McConnell KJ. Blood pressure management of adult patients. In: Baker WL, Beavers C, Bolesta S, et al., eds. ACCP/ASHP 2019 Cardiology Pharmacy Preparatory Review and Recertification Course, 2019. Lenexa, KS: American College of Clinical Pharmacy, 2019:95.

4. Select an appropriate drug therapy regimen
   a. Initiating therapy with a single antihypertensive drug is reasonable in adults with stage 1 HTN and a BP goal of less than 130/80 mm Hg
   b. Initiating antihypertensive drug therapy with two first-line agents of different classes is recommended in adults with stage 2 HTN and an average BP greater than 20/10 mm Hg above their BP target
   c. First-line agents include thiazide diuretics, CCBs, and ACEIs or ARBs.

d. First-line agents for patients with comorbidities is described in Figure 6.

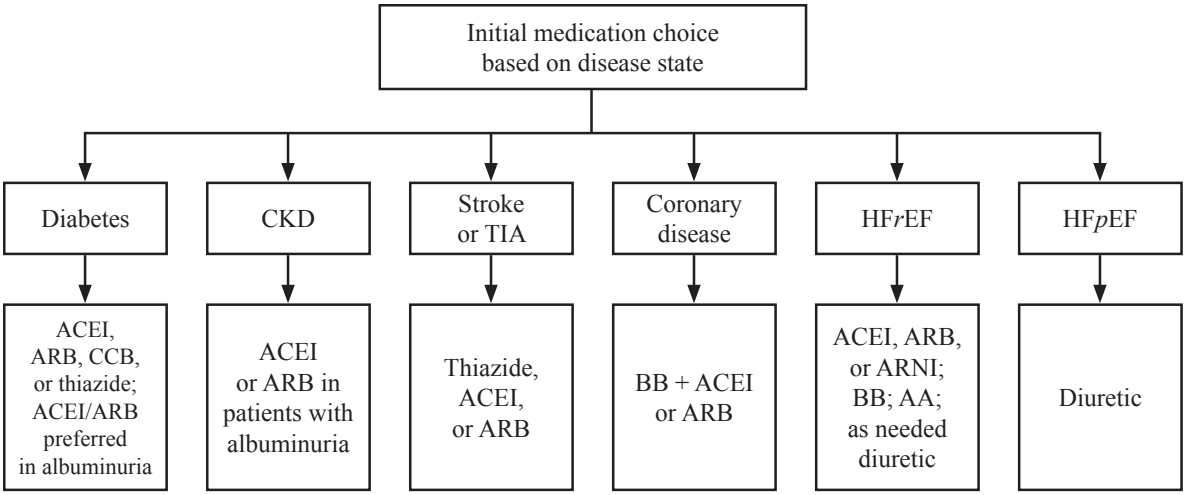


Figure 6. Selecting appropriate therapy for hypertension on the basis of disease state.

AA = aldosterone antagonist; ACEI = angiotensin-receptor converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BB = β-blocker; CCB = calcium channel blocker; CKD = chronic kidney disease; HF*p*EF = heart failure with preserved ejection fraction; HF*r*EF = heart failure with reduced ejection fraction; TIA = transient ischemic attack.

5. Considerations with specific antihypertensive agents
   a. β-Blockers
      i. Caution with asthma or severe chronic obstructive pulmonary disease (especially higher doses) because of pulmonary β-receptor blockade, especially with nonselective β-blockers or high-dose selective β-blockers.
      ii. Greater risk of developing DM than with an ACE inhibitor, ARB, and CCB; use caution in patients at high risk of DM (e.g., family history, obesity)
      iii. Can mask some signs of hypoglycemia in patients with DM
      iv. Can cause depression
   b. Thiazides
      i. Can worsen gout by increasing serum uric acid
      ii. Not recommended for patients with a CrCl less than 30 mL/minute because of reduced efficacy
      iii. Greater risk of developing DM than with ACE inhibitor, ARB, and CCB; use caution in patients at high risk of DM (e.g., family history, obesity)
      iv. Can assist in the management of osteoporosis by preventing urine calcium loss
   c. ACE inhibitors and ARBs
      i. Contraindicated in pregnancy
      ii. Contraindicated with bilateral renal artery stenosis
      iii. Monitor K closely, especially if renal impairment exists or another K-sparing drug or K supplement is used.
   d. Direct renin antagonist (aliskiren)
      i. Contraindicated in pregnancy
      ii. Contraindicated in patients with DM when used in combination with ACE inhibitors or ARBs because of increased risk of renal impairment, hyperkalemia, and hypotension
      iii. Avoid use in combination with cyclosporine or itraconazole.
      iv. Avoid concurrent use with ACE inhibitors or ARBs in patients with renal impairment (CrCl less than 60 mL/minute).

e. Calcium channel blockers
    i. Dihydropyridine CCBs
        (a) Amlodipine, felodipine, nifedipine
        (b) Monitor for peripheral edema, reflex tachycardia, and orthostatic hypotension
        (c) Useful for isolated systolic hypertension or use in African American patients
    ii. Nondihydropyridine CCBs
        (a) Diltiazem, verapamil
        (b) Indicated in hypertensive patients with comorbid conditions which would benefit from HR reduction (e.g., atrial fibrillation, stable angina)
        (c) Contraindicated in heart block and sick sinus syndrome
        (d) Potential drug interactions due to CYP450 inhibition

6. Considerations within specific patient populations
    a. Patients with CHD: Potent vasodilators (hydralazine, minoxidil, and DHP CCBs) may cause reflex tachycardia, thereby increasing myocardial oxygen demand; can attenuate this by also using an AV nodal blocker (β-blocker or non-DHP CCB)
    b. Older adult patients:
        i. Treatment of HTN with an SBP treatment goal of less than 130 mm Hg is recommended for noninstitutionalized ambulatory community-dwelling adults (65 and older) with an average SBP of 130 mm Hg or greater
        ii. For older adults (65 and older) with HTN and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk-benefit is reasonable for decisions regarding intensity of blood pressure lowering and choice of antihypertensives
        iii. The SPRINT trial published in late 2015 showed that targeting an SBP of less than 120 mm Hg, compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major CV events and death from any cause among patients at high risk of CV events but without DM. Twenty-five percent of the study population was older than 75 years.
        iv. Caution with antihypertensive agents and orthostatic hypotension
    c. Black patients: β-Blockers and ACE inhibitors are generally less effective as monotherapy than in non–black patients. In black adults with HTN but without HF or CKD, including those with diabetes mellitus, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. β-blockers and ACE inhibitors should still be used if comorbid conditions dictate.
    d. Women
        i. Oral estrogen-containing contraceptives can increase BP, and the risk can increase with the duration of use.
        ii. HTN increases the risk to mother and fetus in women who are pregnant. Preferred medications include methyldopa, nifedipine, and labetalol. ACE inhibitors, ARBs, and aliskiren should not be used because of the potential for fetal defects.

7. Monitoring
    a. Have the patient return in 4 weeks to assess efficacy (sooner if clinically indicated).
    b. If there is an inadequate response with the first agent with optimal dosing (and adherence is verified) and no compelling indication exists, initiate therapy with a drug from a different class while continuing initial therapy.

8. Resistant HTN
    a. Confirm diagnosis
        i. Office BP of 130/80 mm Hg or greater *and* patient taking at least three antihypertensive medications at optimal doses, including a diuretic (confirmed adherence) <u>*OR*</u>
        ii. Office BP of <130/80 mm Hg but patient requires at least four antihypertensive medications

b. Exclude pseudoresistance
    i. Ensure accurate office BP readings
    ii. Exclude white-coat HTN
    iii. Ensure adherence
c. Identify and reverse contributing factors
    i. Lifestyle factors
        (a) Obesity
        (b) High-salt, low-fiber diet
        (c) Physical inactivity
        (d) Excessive alcohol use
    ii. Interfering medications
        (a) NSAIDs
        (b) Sympathomimetics
        (c) Stimulants
        (d) Oral contraceptives
d. Screen and treat for secondary causes of HTN (described earlier)
e. Assess for target organ damage
f. Pharmacological treatment
    i. Maximize diuretic therapy
        (a) Use thiazide or thiazide-like diuretics if eGFR > 25-30 mL/min/m^2
            (1) Chlorthalidone and indapamide have the most evidence for reducing cardiovascular outcomes
            (2) Chlorthalidone is more effective at inducing predictable natriuresis in patients with an eGFR 30-45 mL/min/m^2
        (b) Use loop diuretics if eGFR < 30 mL/min/m^2
    ii. Add MRA (spironolactone or eplerenone)
    iii. Alter dosing times to include a nocturnal dose or divide doses of drugs with half-lives <12-15 hours
    iv. Add other agents from different drug classes
    v. Addition of hydralazine or minoxidil requires concomitant use of a ß-blocker and diuretic
g. Follow-up
    i. Ensure attainment of target BP after six months of therapy
    ii. If patient not at goal, refer to appropriate specialists

IV. DYSLIPIDEMIA

A. The AHA/ACC released updated Cholesterol Guidelines in 2018 in conjunction with 10 other organizations. Major changes in new guidelines:
    1. Emphasis on personalized risk assessment and shared decision making using tools listed in (D) below
    2. Re-introduction of LDL-C and non-HDL-C goals
    3. Recommendations for statin and nonstatin therapies

B. Goals of Therapy
    1. Reduce CV morbidity and mortality
    2. Achieve LDL-C goals, when appropriate

C. Nonpharmacologic recommendations
    1. Lifestyle modification is cornerstone of initial intervention
    2. Heart-healthy diet

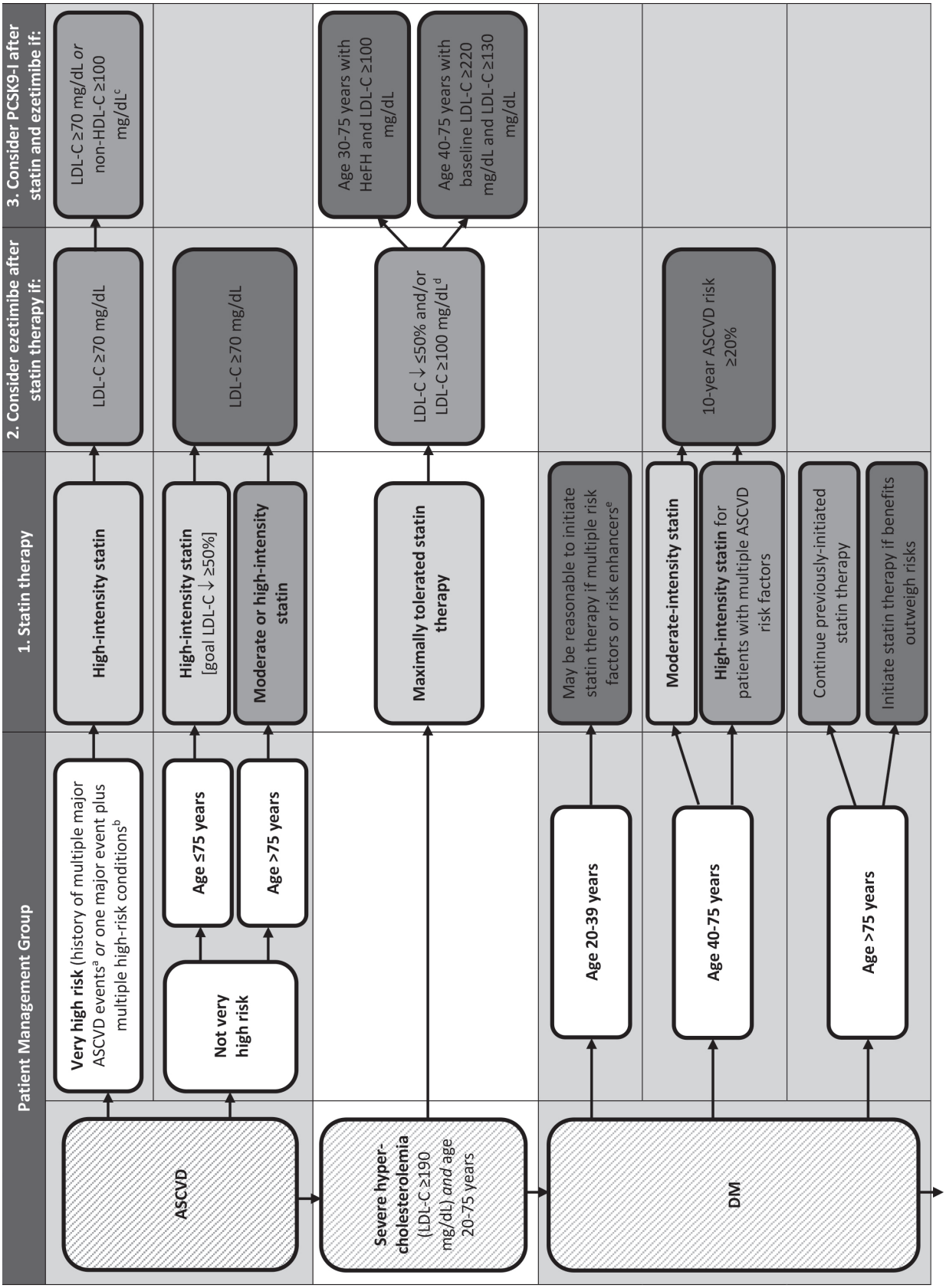
   a. Recommend healthy diets such as the Dietary Approaches to Stop Hypertension (DASH) diet or the Mediterranean Diet
   b. Emphasize consumption of fruits, vegetables, whole grains, low-fat dairy products, skinless poultry and fish, nuts and legumes, and nontropical vegetable oils
   c. Limit sweets, sugar-sweetened beverages, and red meats
   d. Lower intake of saturated fats and replace with unsaturated fats (especially polyunsaturated fats)
3. Regular exercise
4. Engage in moderate-to-vigorous intensity aerobic physical activity 3-4 times per week for an average of 40 minutes per session
5. Smoking cessation

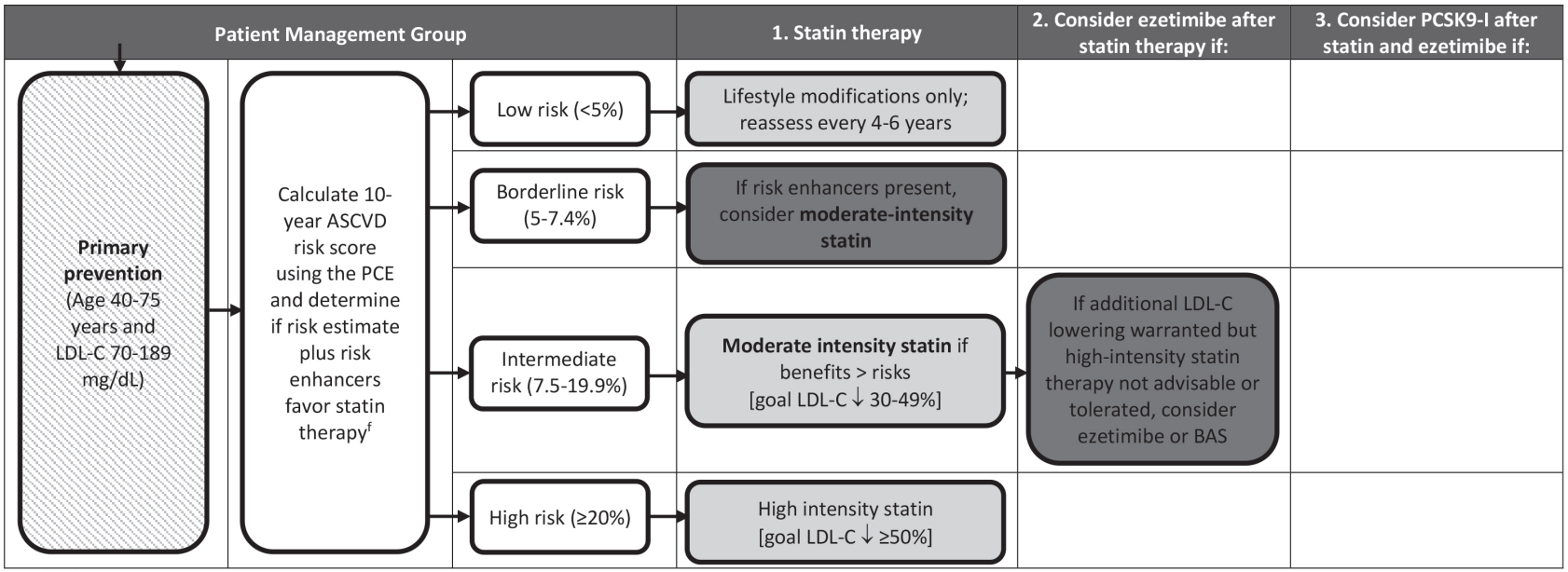
D. Pharmacologic recommendations
   1. Therapy recommendations are divided into patient management groups:
      a. Secondary ASCVD prevention
      b. Severe hypercholesterolemia (LDL-C ≥190 mg/dL)
      c. Diabetes mellitus (DM)
      d. Primary prevention
   2. Pharmacologic management of dyslipidemia is detailed in Figure 7, and general principles are described below:
      a. First, initiate statin therapy if indicated. Optimize statin therapy (high intensity or maximally tolerated dose) before adding nonstatin therapy
      b. Second, add ezetimibe if indicated
      c. Third, consider PCSK9-inhibitors (PCSK9-I)
   3. Special populations
      a. Patients age >75 years
         i. Reasonable to initiate a moderate-intensity statin or continue a moderate- or high-intensity statin if benefits outweigh risks
         ii. Reasonable to discontinue statin therapy if patients have functional decline, multimorbidity, frailty, or reduced life expectancy limits potential benefits
      b. Hypertriglyceridemia
         i. Primary goal is to prevent pancreatitis
         ii. Evaluate for secondary causes (Table 15)

Table 15. Common Secondary Causes of Elevated LDL-C and TG

Cause	Increase LDL-C	Increase TG
Medications	Amiodarone, cyclosporine, diuretics, glucocorticoids	Anabolic steroids, atypical antipsychotics, β-blockers, bile acid sequestrants, glucocorticoids, hormone therapy, protease inhibitors, raloxifine, retinoic acid, sirolimus, tamoxifen, thiazides
Dietary influences	Saturated or *trans* fats, weight gain, anorexia	Very low-fat diets, high carbohydrate intake (refined), excess alcohol, weight gain
Disease states and medical conditions	Nephrotic syndrome, biliary obstruction, hypothyroidism, obesity, pregnancy	Poorly controlled diabetes, hypothyroidism, obesity, pregnancy, nephrotic syndrome, chronic renal failure, lipodystrophies

LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.


Patient Management Group
1. Statin therapy
2. Consider ezetimibe after statin therapy if:
3. Consider PCSK9-I after statin and ezetimibe if:
ASCVD
Very high risk (history of multiple major ASCVD events[a] or one major event plus multiple high-risk conditions[b])
High-intensity statin
LDL-C ≥70 mg/dL
LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL[c]
Not very high risk
Age ≤75 years
High-intensity statin [goal LDL-C ↓ ≥50%]
LDL-C ≥70 mg/dL
Age >75 years
Moderate or high-intensity statin
Severe hyper-cholesterolemia (LDL-C ≥190 mg/dL) and age 20-75 years
Maximally tolerated statin therapy
LDL-C ↓ ≤50% and/or LDL-C ≥100 mg/dL[d]
Age 30-75 years with HeFH and LDL-C ≥100 mg/dL
Age 40-75 years with baseline LDL-C ≥220 mg/dL and LDL-C ≥130 mg/dL
DM
Age 20-39 years
May be reasonable to initiate statin therapy if multiple risk factors or risk enhancers[e]
Age 40-75 years
Moderate-intensity statin
High-intensity statin for patients with multiple ASCVD risk factors
10-year ASCVD risk ≥20%
Age >75 years
Continue previously-initiated statin therapy
Initiate statin therapy if benefits outweigh risks


Patient Management Group
1. Statin therapy
2. Consider ezetimibe after statin therapy if:
3. Consider PCSK9-I after statin and ezetimibe if:
Primary prevention (Age 40-75 years and LDL-C 70-189 mg/dL)
Calculate 10-year ASCVD risk score using the PCE and determine if risk estimate plus risk enhancers favor statin therapy[f]
Low risk (<5%)
Lifestyle modifications only; reassess every 4-6 years
Borderline risk (5-7.4%)
If risk enhancers present, consider moderate-intensity statin
Intermediate risk (7.5-19.9%)
Moderate intensity statin if benefits > risks [goal LDL-C ↓ 30-49%]
If additional LDL-C lowering warranted but high-intensity statin therapy not advisable or tolerated, consider ezetimibe or BAS
High risk (≥20%)
High intensity statin [goal LDL-C ↓ ≥50%]

Key: Class I (strong) recommendation
Class IIa (moderate) recommendation; therapy is reasonable
Class IIb (weak) recommendation; therapy may be considered

ABI = ankle-brachial index; ASCVD = atherosclerotic cardiovascular disease; BAS = bile acid sequestrant; DM = diabetes mellitus; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; PCE = Pooled Cohort Equation; PCSK9-I = PCSK9 inhibitor

[a]Major ASCVD events are acute coronary syndrome (ACS) within the past 12 months, other history of myocardial infarction (MI), history of ischemic stroke, and symptomatic peripheral arterial disease

[b]High risk conditions are age ≥65 years, heterozygous familial hypercholesterolemia, history of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s), diabetes mellitus (DM), hypertension, chronic kidney disease (eGFR 15-59 mL/min/1.73m^2), current smoking, history of congestive heart failure, and persistently elevated LDL-C ≥ 100 mg/dL despite maximally tolerated statin therapy and ezetimibe

[c]Clinical evidence supports addition of PCSK9-I after maximally tolerated statin therapy, but adding ezetimibe first is more cost effective

[d]May consider adding a BAS to statin and ezetimibe if LDL-C reduction is <50% and fasting triglycerides ≤300 mg/dL, especially if ineligible for PCSK9-I therapy

[e]DM-specific risk enhancers include DM of long duration (≥ 10 years with type 2 DM or ≥ 20 years with type 1 DM); microvascular complications (albuminuria [≥ 30 mcg/mg creatinine], eGFR <60 mL/min/1.73m^2, retinopathy, or neuropathy); or ankle-brachial index < 0.9

[f]If risk decision is uncertain (especially borderline and intermediate risk patients), consider measuring coronary artery calcium

Source: Grundy SM, Stone NJ, Bailey AL, et al. 2018 ACC/AHA/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2018;Nov 10:[Epub ahead of print]

Figure 7. Algorithm for statin and non-statin therapy recommendations based on patient management group.

iii. Moderate hypertriglyceridemia (triglycerides [TG] 175-499 mg/dL)
   (a) Address and treat lifestyle factors, comorbidities, and medications which increase TGs
   (b) If persistently elevated and ASCVD risk ≥7.5%, consider initiation or intensification of statin therapy
iv. Severe hypertriglyceridemia (TG ≥ 500 mg/dL)
   (a) If persistently elevated and ASCVD risk ≥7.5%, consider initiation or intensification of statin therapy
   (b) Reasonable to initiate fibrate therapy to prevent acute pancreatitis, especially if fasting TG ≥ 1000 mg/dL
v. Expected changes in TG concentrations with drug therapy (Table 16)

Table 16. Effect of Lipid-Lowering Medications on TG

Medication	% Decrease in TG
Statins	7–30
Fibrates	20–50
Niacin	20–50
Ezetimibe	5–11
Omega-3 fatty acids	19–44

TG = triglycerides

E. Risk assessment tools for primary prevention
   1. Risk discussions and shared decision making with patients should consider whether lifestyle and ASCVD risk factors have been addressed, cost considerations, and a discussion of the potential benefits and adverse events of drug therapy. Patients and health care professionals should work together to establish a customized cholesterol management plan.
   2. Pooled Cohort Equation (PCE) to estimate 10-year ASCVD risk
      a. Measures hard ASCVD events: fatal and nonfatal MI and stroke
      b. Assists with identifying higher-risk patients for statin therapy
      c. Should not be used for patients with clinical ASCVD
      d. Available at http://tools.acc.org/ASCVD-Risk-Estimator/
      e. Components of PCE:
         i. Sex
         ii. Age
         iii. Race
         iv. TC
         v. HDL-C
         vi. SBP
         vii. Receiving treatment for high BP
         viii. DM
         ix. Smoker
   3. Risk-enhancing factors
      a. Family history of premature ASCVD (males <55 years, females <65 years)
      b. Primary hypercholesterolemia (LDL-C 160-189 mg/dL or non-HDL-C 190-219 mg/dL)
      c. Metabolic syndrome
      d. Chronic kidney disease

e. Chronic inflammatory conditions such as psoriasis, rheumatoid arthritis, HIV/AIDS
f. History of premature menopause (age <40 years)
g. History of preeclampsia
h. High-risk race/ethnicity (e.g., South Asian ancestry)
i. Elevated TG ≥175 mg/dL
j. Elevated biomarkers such as high-sensitivity C-reactive protein, lipoprotein (a), apolipoprotein B
k. Ankle-brachial index <0.9

4. Coronary artery calcium (CAC) score for additional risk-stratification
   a. If risk decision is uncertain (especially borderline and intermediate risk patients), consider measuring coronary artery calcium
   b. Score = 0: consider no statin (unless DM, family history of premature coronary heart disease, or cigarette smoking present)
   c. Score = 1-99: favors statin if age ≥55
   d. Score ≥100 *or* ≥75th percentile: favors statin

F. Monitoring
   1. Measure fasting lipids 4-12 weeks after therapy initiation
   2. Measure fasting lipids every 3-12 months thereafter
   3. Periodically re-assess risk factors for ASCVD

G. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins)
   1. General approach to initiating statin therapy:
      a. Fasting lipid panel
         i. If baseline LDL-C is higher than 190 mg/dL, evaluate for secondary causes. If primary, screen for familial hypercholesterolemia.
         ii. If baseline TG 500 mg/dL or higher, treat hypertriglyceridemia
      b. Alanine aminotransferase (ALT)
         i. Evaluate patients with unexplained ALT more than 3x upper limit of normal
      c. Hemoglobin A1C
      d. Creatine kinase (if indicated)
      e. Evaluate for secondary causes or conditions that may affect statin safety
   2. Efficacy
      a. First line for high LDL-C or CHD risk
      b. When selecting a statin, consider its intensity (Table 17).
      c. Reduce LDL-C by 24%–60%.
      d. Reduce TG by 7%–30%.
      e. Raise HDL-C by 5%–15%.
      f. Reduce major coronary events.
      g. Reduce CHD mortality.
      h. Reduce coronary procedures (percutaneous coronary intervention [PCI] or coronary artery bypass grafting).
      i. Reduce stroke.
      j. Reduce total mortality.

Table 17. Relative LDL-C-Lowering Efficacy of Statins

Atorva (mg)	Fluva (mg)	Pitava (mg)	Lova (mg)	Prava (mg)	Rosuva (mg)	Simva (mg)	%↓ LDL
—	20–40	1	20	10–20	—	10	30
10	80	2	40	40	—	20	38
20	—	4	80	80	5	40	41
40	—	—	—	—	10	—	47
80	—	—	—	—	20	—	55
—	—	—	—	—	40	—	63

Denotes low-intensity statin; lowers LDL-C by < 30%.
Denotes moderate-intensity statin; lowers LDL-C by 30% to < 50%.
Denotes high-intensity statin; lowers LDL-C by ≥ 50%.

Atorva = atorvastatin; Fluva = fluvastatin; LDL-C = low-density lipoprotein cholesterol; Lova = lovastatin; Pitava = pitavastatin; Prava = pravastatin; Rosuva = rosuvastatin; Simva = simvastatin.

Adapted from: Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. Circulation 2014;129(suppl 2):S1-45.

3. Mechanism of action: Inhibits enzyme responsible for converting HMG-CoA to mevalonate (rate-limiting step in production of cholesterol)
4. Main adverse effects and monitoring
    a. Myopathy (can check creatine kinase [CK] at baseline and then only if muscle symptoms occur; no regular monitoring)
    b. Elevated liver enzymes
        i. Obtain LFTs at baseline in all patients
        ii. Perform repeated LFTs only when clinically indicated.
        iii. Monitor for symptoms of hepatic injury.
5. Absolute contraindications
    a. Active liver disease, unexplained persistent elevations in hepatic transaminases
    b. Pregnancy
    c. Nursing mothers
    d. Certain medications (agent-specific; see drug interactions below)
6. Select drug interactions (see Table 18)
    a. Fibrates: Increased risk of myopathy and rhabdomyolysis when coadministered with statins. Risk is greater with gemfibrozil than with fenofibrate.
    b. Niacin: Doses greater than 1 g/day increase the risk of myopathy and rhabdomyolysis when used concomitantly with statins; risk is lower than with fibrates; statins and niacin are commonly used together; monitor for muscle pain.
    c. Canagliflozin: A case report of a myopathy attributed to a drug interaction between canagliflozin and rosuvastatin was recently reported.
7. Differences exist between statins in regard to pharmacokinetics and renal dosing (Tables 19 and 20)

Table 18. Select Drug Interactions with Statins

	Lovastatin	Pravastatin	Simvastatin	Fluvastatin	Pitavastatin	Atorvastatin	Rosuvastatin
Amiodarone	Daily dose NTE 40 mg		Daily dose NTE 20 mg				
Amlodipine			Daily dose NTE 20 mg				
Azole antifungals	CI (itraconazole, ketoconazole, posaconazole, and voriconazole)		CI (itraconazole, ketoconazole, posaconazole, and voriconazole)	Daily dose NTE 20 mg BID (fluconazole)		Daily dose NTE 20 mg (itraconazole)	
Bempedoic acid		Daily dose NTE 40 mg	Daily dose NTE 20 mg				
Cobicistat-containing products	CI		CI				
Colchicine	Use with caution	Use with caution	Use with caution	Use with caution	Use with caution	Use with caution	Use with caution
Cyclosporine	Avoid use	Daily dose NTE 20 mg	CI	Daily dose NTE 20 mg BID	CI	Avoid use	Daily dose NTE 5 mg
Danazol	Daily dose NTE 20 mg		CI				
Diltiazem Verapamil	Daily dose NTE 20 mg		Daily dose NTE 10 mg				
Dronedarone	Daily dose NTE 20 mg		Daily dose NTE 10 mg				
Erythromycin Clarithromycin	CI	Daily dose NTE 40 mg (clarithromycin)	CI		Daily dose NTE 1 mg (erythromycin)	Daily dose NTE 20 mg (clarithromycin)	
Gemfibrozil	Avoid use	Avoid use	CI	Avoid use	Avoid use	Avoid use	Daily dose NTE 10 mg
Grapefruit juice (> 1 quart per day)	Avoid use		Avoid use			Avoid excess quantities (> 1.2 L/day)	
Lomitapide	Consider lovastatin dose reduction		Daily dose NTE 20 mg (or 40 mg if tolerated 80 mg for ≥1 yr)				
Nefazodone	CI		CI				
Niacin	Avoid doses of niacin ≥ 1 g/day	Avoid doses of niacin ≥ 1 g/day	Avoid doses of niacin ≥ 1 g/day	Avoid doses of niacin ≥ 1 g/day	Avoid doses of niacin ≥ 1 g/day	Avoid doses of niacin ≥ 1 g/day	Use with caution
HIV protease inhibitors	CI		CI			Avoid use with tipranavir plus ritonavir. Daily dose NTE 20 mg (saquinavir/ ritonavir, darunavir/ ritonavir, fosamprenavir or fosamprenavir/ ritonavir) Daily dose NTE 40 mg (nelfinavir)	Daily dose NTE 10 mg (lopinavir/ ritonavir or atazanavir/ ritonavir)
Ranolazine	Consider dose adjustment		Daily dose NTE 20 mg				
Rifampin					Daily dose NTE 2 mg		

BID = twice daily;

CI = contraindicated; HIV = human immunodeficiency virus; NTE = not to exceed.

Table 19. Pharmacokinetic Differences Between Statins

	Bioavailability (%)	Half-life (hr)	Elimination/ Metabolism	Prodrug	Solubility
Atorvastatin	14	14	3A4	No	Lipophilic
Fluvastatin	24	3	2C9	No	Lipophilic
Lovastatin	< 5	2–3	3A4	Yes	Lipophilic
Pitavastatin	43-51	12	2C9	No	Lipophilic
Pravastatin	17	1.8	N/A	No	Hydrophilic
Simvastatin	< 5	2	3A4	Yes	Lipophilic
Rosuvastatin	20	19	2C9	No	Hydrophilic

N/A = not applicable.

Table 20. Dosing of Statin Agents in CKD

Drug	Comments	Dose Recommended by KDIGO Guidelines[a]
Atorvastatin	—	20 mg/day
Fluvastatin	Doses > 40 mg/day not studied in severe renal impairment	80 mg/day
Lovastatin	CrCl <30 mL/min: NTE 20 mg/day	Not studied
Pitavastatin	CrCl 15-59 mL/min: NTE 2 mg/day	2 mg/day
Pravastatin	CrCl <30 mL/min: Initial dose = 10 mg/day	40 mg/day
Simvastatin[b]	CrCl < 30 mL/min: Initial dose = 5 mg/day	40 mg/day (ezetimibe/simvastatin 10/20 mg/day)
Rosuvastatin	CrCl < 30 mL/min: NTE 10 mg/day	10 mg/day

[a]Recommendations for Stage 3a through Stage 5 CKD (from Kidney Disease: Improving Global Outcomes Lipid Work Group. KDIGO clinical practice guidelines for lipid management in chronic kidney disease. Kidney Int 2013;3:1-56).

[b]The 80-mg dose of simvastatin should be reserved for patients who have been taking simvastatin 80 mg long term (e.g., ≥ 12 mo) and who are without evidence of muscle toxicity.

CrCl = creatinine clearance; NTE = not to exceed

H. Ezetimibe
   1. Efficacy
      a. Lowers LDL-C by 18%–20%
      b. Can raise HDL-C by 1%–5%
      c. Lowers TG by 5%–10%
   2. Mechanism of action: Inhibition of cholesterol absorption
   3. Adverse effects and monitoring: Diarrhea, upper respiratory tract symptoms; no monitoring necessary
   4. Data suggest that combination with simvastatin is superior to simvastatin alone in prevention of CV events.

I. PCSK9 Inhibitors
   1. Efficacy: Lower LDL-C by an additional 45%–68% when combined with statin therapy; reduce CV events when added to statin therapy (FOURIER and ODYSSEY OUTCOMES trials)
   2. Mechanism of action: Monoclonal antibodies that inhibit a protein called PCSK9, increasing cholesterol clearance from the liver
   3. Both indicated for heterozygous familial hypercholesterolemia or clinical ASCVD; evolocumab also indicated for homozygous familial hypercholesterolemia (HoFH)

4. PCSK9 Inhibitors are only indicated for select patients already receiving maximally tolerated statin therapy and ezetimibe with either clinical ASCVD at very high risk or severe hypercholesterolemia in the 2018 ACC/AHA cholesterol guidelines (Figure 7)
5. Adverse effects: Injection-site reactions, respiratory infections
6. Dose:
    a. Evolocumab:
        i. Heterozygous familial hypercholesterolemia or clinical ASCVD: 140 mg subcutaneously every 2 weeks or 420 mg subcutaneously once monthly
        ii. Homozygous familial hypercholesterolemia: 420 mg subcutaneously once monthly
    b. Alirocumab: Initial dose, 75 mg subcutaneously every 2 weeks or 300 mg subcutaneously every 4 weeks; if LDL-C reduction inadequate, can adjust dose to 150 mg subcutaneously every 2 weeks

J. Bile acid sequestrants (cholestyramine, colestipol, colesevelam)
1. Efficacy
    a. Reduce LDL-C by 15%–27%.
    b. Raise HDL-C by 3%–5%.
    c. May increase TG concentrations.
    d. Reduce major coronary events.
2. Mechanism of action: Bind to bile acids to disrupt enterohepatic recirculation of bile acids. Liver is stimulated to convert hepatocellular cholesterol to bile acids.
3. Adverse effects: GI distress, constipation
4. Decreased absorption of many drugs including: warfarin, amiodarone, levothyroxine, ezetimibe, digoxin, and thiazides; administer drugs 1–2 hours before or 4 hours after bile acid sequestrant
5. Contraindications: Complete biliary obstruction, raised TG concentrations (especially greater than 400 mg/dL)

K. Niacin (Table 21)
1. Efficacy
    a. Lowers LDL-C by 5%–25%
    b. Lowers TG by 20%–50%
    c. Raises HDL-C by 15%–35%
    d. Reduces major coronary events
    e. Lowers lipoprotein (a)
2. Mechanism of action: Inhibits mobilization of free fatty acids from peripheral adipose tissue to the liver and reduces synthesis of TG, very-low-density lipoproteins, and LDL-C
3. Adverse effects and monitoring: Flushing, hyperglycemia, hyperuricemia, myopathy, upper GI distress, increased hepatic transaminases; monitor LFTs at baseline, every 6–12 weeks for first year and then yearly
4. Sustained release appears to be more hepatotoxic than extended-release or immediate-release preparations.
5. Extended-release niacin is less likely to cause flushing.
6. Contraindications: liver disease and active peptic ulcer disease. Caution in patients predisposed to gout
7. Flushing can be minimized by taking aspirin or an NSAID 30–60 minutes before niacin, taking at bedtime with food, using slow titration, and avoiding hot beverages, spicy foods, and hot showers around the time of administration.
8. According to the 2018 AHA/ACC cholesterol guidelines, there are no clear indications for routine niacin use for reduction of LDL-C.

Table 21. Niacin Formulations

Drug Form	Brand Name	Dose Range (g)
Immediate release	Niacin, Niacor	1.5–6
Extended release	Niaspan	1–2
Sustained release	Slo-Niacin	1–2

L. Fibrates
   1. Efficacy
      a. Lower LDL-C by 5%–20% (with normal TG)
      b. May raise LDL-C with very high TG
      c. Lower TG by 20%–50%
      d. Raise HDL-C by 10%–20%
   2. Mechanism of action: Reduces rate of lipogenesis in the liver
   3. Adverse effects and monitoring: Dyspepsia, gallstones, myopathy, increased hepatic transaminases. Monitor LFTs every 3 months during first year and then periodically.
   4. Contraindications: Severe renal or hepatic disease, pre-existing gallbladder disease
   5. Indicated for treatment of severe hypertriglyceridemia, especially in patients with TG ≥ 1000 mg/dL

M. Omega-3 fatty acids
   1. Contain varying ratios of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
      a. Omega-3 acid ethyl esters: DHA and EPA
      b. Icosapent ethyl: EPA only
      c. Omega-3 carboxylic acid: DHA and EPA
   2. Efficacy
      a. Lowers TG by 26%–45%
      b. Can raise LDL-C when TG concentrations are high
      c. Raises HDL-C by 5%–14%
      d. Icosapent ethyl reduced the composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina in the REDUCE-IT trial.
   3. Mechanism of action: Reduction of hepatic production of very-low-density lipoproteins; possible reduction in hepatic synthesis of TG; increased hepatic β-oxidation
   4. Adverse effects: Arthralgia, GI effects (e.g., burping, taste perversion, dyspepsia); at more than 3 g/day, bleeding (because of inhibition of platelet aggregation)
   5. Dose: 2–4.8 g/day as a single dose or in two divided doses

N. Bempedoic Acid
   1. Efficacy
      a. Lowers LDL-C by 21%
      b. Reduces HDL-C by 5%
   2. Mechanism of action: Inhibits ATP-citrate lyase, which inhibits cholesterol synthesis in the liver
   3. Adverse effects and monitoring: Gout, hyperuricemia, leukopenia, thrombocytopenia, tendon rupture. Monitor for signs/symptoms of hyperuricemia and tendon rupture.
   4. Indicated for use as an adjunct to statin therapy in heterozygous familial hypercholesterolemia or known CV disease in patients who require additional LDL-C reduction

Patient Cases

8. M.M. is a 63-year-old white woman who just finished 6 months of diet and exercise for dyslipidemia. She has a history of hypertension, DM, and asthma. She smokes one pack of cigarettes and drinks three beers per day. Her mother had HTN and suffered an MI at age 42 years. Her father had HTN and DM. Her medications are albuterol metered dose inhaler, lisinopril, metformin, linagliptin, and calcium carbonate antacids. Her vital signs include BP 134/84 mm Hg and HR 75 beats/minute. Her laboratory results are as follows: HDL-C 38 mg/dL, LDL-C 134 mg/dL, TG 186 mg/dL, TC 209 mg/dL, and hemoglobin A1C 8.6%. Her pooled cohort equation estimates a 10-year ASCVD risk of 27.8%. What is the most appropriate next step for M.M.?
   A. Initiate a low-intensity statin
   B. Initiate a moderate-intensity statin
   C. Initiate a high-intensity statin
   D. Initiate a high-intensity statin plus ezetimibe

9. According to the ACC/AHA blood cholesterol guidelines, which is best described as a high-intensity statin dose?
   A. Pravastatin 20 mg/day.
   B. Lovastatin 20 mg/day.
   C. Atorvastatin 40 mg/day.
   D. Rosuvastatin 10 mg/day.

10. Which best describes a potential secondary cause of high TG concentrations?
   A. Amiodarone.
   B. Biliary obstruction.
   C. Sirolimus.
   D. Saturated fats.

V. CHRONIC CORONARY HEART DISEASE AND CHRONIC STABLE ANGINA

CHD is a general term that does not discriminate between the various phases the individual may cycle between for several decades. These phases include asymptomatic disease, stable angina, progressive angina, unstable angina, non–ST-segment elevation MI, and ST-segment elevation MI.

Depending on the patient's manifestations, some therapies may be added or modified. However, several basic treatment rules apply to all individuals with CHD, regardless of the symptoms they may experience.

The following mnemonic, developed for patients with chronic stable angina, can be applied to all patients with CHD.

A = Aspirin and antianginal therapy
B = β-Blocker and BP
C = Cigarette smoking and cholesterol
D = Diet and DM
E = Education and exercise

Although not all patients with CHD have DM or smoke cigarettes, the mnemonic is a way to remember the primary areas that should be addressed, as applicable, in all patients with CHD.

Some important recommendations:

- Weight reduction and maintenance to a body mass index of 18.5–24.9 kg/m^2 and a waist circumference less than 40 inches for male patients and less than 35 inches for female patients
- Physical activity for 30–60 minutes/day, 7 days/week (minimum of 5 days/week)
- BP control
- Alcohol consumption should be limited to 1 drink (120 mL [4 ounces] of wine, 360 mL [12 ounces] of beer, or 30 mL [1 ounce] of spirits) per day for women and 1 or 2 drinks per day for men.
- No smoking and no environmental exposure to smoke
- Reduced intake of saturated fats (to less than 7% of total calories), *trans* fatty acids (to less than 1% of total calories), and cholesterol (to less than 200 mg/day)
- If a patient has DM, A1C less than 7%; a goal A1C of 7%–9% is reasonable in certain patients according to age, history of hypoglycemia, presence of microvascular or macrovascular complications, or comorbid conditions.
- Annual influenza vaccine

Patient Case

11. A 66-year-old man with a medical history of HTN and acute coronary syndrome with a drug-eluting coronary stent placement 14 months ago presents to the primary care clinic. Current medications include aspirin 81 mg/day, prasugrel 10 mg/day, nitroglycerin 0.4-mg sublingual tablets as needed for chest pain, metoprolol succinate 75 mg/day, ramipril 10 mg/day, and atorvastatin 20 mg/day. He asks you how long he will need to take prasugrel. What is the best answer?

    A. Call your physician because you may be able to stop prasugrel now.

    B. Your prasugrel should have been discontinued 6 months after acute coronary syndrome; discontinue it now.

    C. You will need to take prasugrel indefinitely.

    D. You will need to take prasugrel for at least 18 months after your MI and stent placement.

Therapeutic Management of CHD

A. Aspirin for Stable CHD
    1. Indicated in all patients with CHD unless contraindicated
    2. Dose: 75–162 mg/day
    3. Decreases CV events by about one third
    4. Clopidogrel 75 mg/day can be used if aspirin contraindicated (e.g., allergy)

B. Antiplatelet therapy for stable CHD for patients undergoing PCI
    1. Aspirin is indicated in all patients.
    2. A $P2Y_{12}$ is indicated in patients who undergo PCI with stenting; clopidogrel is the only $P2Y_{12}$ inhibitor recommended in the stable ischemic heart disease (SIHD) guidelines.

Table 22. Recommendations for Dosing and Duration of Antiplatelet Therapy in SIHD

Clinical Scenario	Aspirin		$P2Y_{12}$ Inhibitors	
	Initial Dose	Subsequent Doses (Starting Day 2) and Therapy Duration	Recommended Minimum Treatment Duration (Class I)[a]	Alternative Treatment Options (Class IIb)[b,c]
SIHD treated with PCI and BMS placed	325 mg before PCI	75–100 mg/day indefinitely	Clopidogrel for 1 month	Reasonable to extend clopidogrel for > 1 month for those at low risk of bleeding
SIHD treated with PCI and DES placed	325 mg before PCI	75–100 mg/day indefinitely	Clopidogrel for 6 months	Reasonable to discontinue clopidogrel after 3 months in those at high risk of bleeding or those who experience significant overt bleeding[d]
				Reasonable to extend clopidogrel for > 6 mo for those at low risk of bleeding[d]

[a]Class I recommendation; defined as "should be given."

[b]Class IIb recommendation; defined as "may be considered."

[c]Each patient should be evaluated for his or her individual ischemic/bleeding risk, preferences, cost, etc., to determine the ideal duration of dual antiplatelet therapy.

[d]The DAPT Score detailed in Acute Care in Cardiology I may be used to guide decisions regarding thrombotic versus bleeding risk

BMS = bare metal stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; PCI = percutaneous coronary intervention; SIHD = stable ischemic heart disease.

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C. Lipid-lowering therapy (see section IV: Dyslipidemia)
   1. Counsel on healthy lifestyle habits
   2. Lipid panel, baseline alanine aminotransferase; consider secondary causes of dyslipidemia, evaluate for conditions that may influence statin safety
   3. High-intensity statin therapy if without contraindications, drug–drug interactions, or history of statin intolerance (class I recommendation)

D. ACE Inhibitors
   1. Greatly decrease CV events in patients with CHD (and no left ventricular dysfunction) at high risk of subsequent CV events.
   2. Should be considered in all patients who also have an LVEF of 40% or less, HTN, DM, and/or CKD (class I recommendation)
   3. Consider using in lower-risk patients with a mildly reduced or normal LVEF in whom CV risk factors are well controlled and revascularization has been performed (class IIb recommendation).

E. ARBs: Recommended as an alternative to ACE inhibitors in patients who also have an LVEF of 40% or less, HTN, DM, or CKD or who are unable to tolerate an ACE inhibitor (e.g., cough or angioedema; class IIa recommendation)

F. Additional therapies for chronic stable angina
   1. Definition: Predictable angina symptoms with exertion
   2. Goals: Reduce symptoms of ischemia, increase physical function, and improve quality of life. In general, achieved by either decreasing myocardial oxygen demand or increasing myocardial oxygen supply
   3. Specific agents
      a. β-Blockers
         i. Pharmacologic effects: Decreased inotropy and HR (decrease oxygen demand)
         ii. Goal resting HR 55–60 beats/minute (less than 50 beats/minute if angina symptoms continue)
         iii. Goal exercise HR of no more than 75% HR associated with angina symptoms
         iv. Place in therapy: May be considered chronic therapy for all patients with coronary or other vascular disease. Should be prescribed first-line for relief of angina symptoms in patients with stable ischemic heart disease (class I). Also a class I indication for first 3 years post-MI
         v. Contraindications: Severe bradycardia (HR less than 50 beats/minute), high-degree AV block or sick sinus syndrome (in absence of a pacemaker)
      b. CCBs
         i. Pharmacologic effects
            (a) Decrease coronary vascular resistance and increase coronary blood flow (increase oxygen supply)
            (b) Negative inotropy, to varying degrees; nifedipine much greater than amlodipine and felodipine (decrease oxygen demand)
            (c) Decrease HR (verapamil and diltiazem only; decrease oxygen demand)
         ii. Place in therapy
            (a) Non-DHP CCBs may be added to β-blocker therapy to achieve HR goals (caution advised; combination can cause heart block).
            (b) Instead of β-blocker therapy when unacceptable adverse effects emerge or if treating Prinzmetal's angina
            (c) Short-acting CCBs (nifedipine) have been associated with increased CV events; should be avoided (except in slow-release formulations)
         iii. Contraindications for non-DHP CCBs: HF*r*EF, severe bradycardia, high-degree AV block or sick sinus syndrome (in absence of a pacemaker)
      c. Nitrates
         i. Pharmacologic effects:
            (a) Endothelium-dependent vasodilation, dilates epicardial arteries and collateral vessels (increase oxygen supply)
            (b) Decreased left ventricular volume because of decreased preload mediated by venodilation (decrease oxygen demand)
         ii. Place in therapy
            (a) A scheduled long-acting nitrate is useful in conjunction with a β-blocker or non-DHP CCB, or both (to blunt the reflex sympathetic tone with nitrate therapy).
            (b) As-needed sublingual tablets, powder, or spray nitroglycerin is necessary to relieve effort or rest angina.
            (c) In addition, as-needed sublingual tablets, powder, or spray nitroglycerin can be used before exercise to avoid ischemic episodes.
         iii. Caution: Hypertrophic obstructive cardiomyopathy, inferior wall MI, severe aortic valve stenosis, avanafil within 12 hours, sildenafil and vardenafil within 24 hours, tadalafil within 48 hours

d. Ranolazine
    i. Pharmacologic effects
        (a) Inhibits the late phase of the inward Na channel in ischemic myocytes during repolarization, leading to a reduction in intracellular Na concentrations. This reduction in Na concentrations leads to reduced calcium influx, which decreases ventricular tension and myocardial oxygen consumption.
        (b) Increases "oxygen efficiency"
    ii. Place in therapy
        (a) Ideal role is unclear
        (b) Use in combination with β-blockers, CCBs, and/or nitrates when initial management with these drugs is unsuccessful.
        (c) Use when BP or HR is too low to add β-blockers, CCBs, and/or nitrates
        (d) Modest reduction in hemoglobin A1C
        (e) Important points
            (1) No significant effects on HR or BP; thus, bradycardia and hypotension are not of concern
            (2) Dose-related QT interval prolongation
            (3) Metabolized by CYP3A; P-gp substrate
                (A) Avoid in hepatic dysfunction.
                (B) Avoid use with strong CYP3A inhibitors, including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir.
                (C) Avoid use with CYP3A inducers such as rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, or St. John's wort.
                (D) Limit the dose to 500 mg twice daily in patients receiving moderate CYP3A4 inhibitors, including diltiazem, verapamil, erythromycin, fluconazole, and grapefruit juice.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

This patient has NYHA class III HF*r*EF with an LVEF of 20%. The best option is to increase her carvedilol dose to the goal dose of 25 mg twice daily (Answer A). Despite her HR of 68 beats/minute, it is safe to increase the β-blocker. Higher carvedilol doses have been associated with reductions in mortality. Appropriate monitoring would include signs and symptoms of hypotension and bradycardia. Her ACE inhibitor is already at the maximum recommended lisinopril dose for heart failure; therefore, further increases are not warranted (Answer B). Spironolactone 25 mg/day is the recommended dose for patients with HF*r*EF who are already receiving an ACE inhibitor and a β-blocker and are NYHA class III. Increasing the spironolactone dose to 50 mg/day is unwarranted (Answer C). Her digoxin concentration of 0.7 ng/dL is within the desired range of 0.5–0.9 ng/mL; therefore, no dose increase is warranted, because this would not improve efficacy and would only increase the risk of toxicity (Answer D).

2. Answer: B

Increasing the ACE inhibitor to target doses should be achieved in all patients, if possible. This patient's BP of 120/70 mm Hg safely permits increasing enalapril from 5 to 10 mg twice daily, making Answer B correct. The patient's SCr does not prevent the enalapril dose from being titrated because it is stable, and he does not have hyperkalemia. There is no consensus that carvedilol is preferred to extended-release metoprolol for patients with HF*r*EF (Answer A). Spironolactone is not appropriate to initiate in this patient because his baseline SCr concentration is greater than 2.5 mg/dL (Answer C). Digoxin should be added only in patients who continue to have symptoms or hospitalizations despite therapy with an ACE inhibitor, β-blocker, and diuretic. Additionally, digoxin 0.125 mg daily would likely be too high for a patient with a SCr of 2.8 mg/dL. This patient's ACE inhibitor therapy is not considered optimal (Answer D).

3. Answer: C

Cilostazol, a phosphodiesterase type 3 inhibitor, may be associated with an elevated risk of ventricular arrhythmias and death in patients with HF*r*EF (Answer C). Acetaminophen is the drug of choice for mild to moderate pain in patients with HF, because NSAIDs can lead to water retention and worsening HF symptoms (Answer A). The selective serotonin reuptake inhibitors are not contraindicated in HF (Answer B). Properly dosed thyroid replacement therapy, as evidenced by his therapeutic thyroid-stimulating hormone concentration, is also beneficial because both hypothyroidism and hyperthyroidism have negative consequences in patients with HF (Answer D).

4. Answer: D

This patient's ventricular rate is well controlled with his metoprolol tartrate therapy; therefore, no additional AV nodal blockade is warranted with either a non-dihydropyridine CCB (Answer B) or digoxin (Answer A). This patient with AF would be considered at high risk of a stroke because of his history of HTN and TIA. Given these risk factors, this patient has a CHA_2DS_2-VASc score of 3; therefore, anticoagulation with an oral anticoagulant agent is indicated. Warfarin titrated to a goal INR of 2.5 would be a potentially appropriate option; however, this patient may be unable to travel to his primary care provider's office for weekly INR checks (Answer C). In this case, dabigatran 150 mg twice daily (Answer D) may be the best choice because it does not warrant INR monitoring, the patient has prescription insurance, he appears to be adherent to a twice-daily medication regimen already, and he does not have renal impairment.

5. Answer: C

With the new diagnosis of HF*r*EF, this patient can no longer receive sotalol. Discontinuing this medication is important so that his risk of arrhythmic death is not increased. Adding metoprolol is a reasonable approach, but not until his HF has been properly controlled, making both Answers A and D incorrect. If rhythm control is desired, amiodarone and dofetilide are the only two antiarrhythmic drugs that have been proved safe and effective in patients with HF*r*EF, making Answer C correct. Of importance, drug interactions exist between amiodarone, digoxin, and warfarin, which will need to be addressed. Dronedarone (Answer B) is not recommended in patients with symptomatic HF with a recent decompensation.

6. Answer: B

W.D.'s blood pressure falls into the stage 2 HTN category. The ACC/AHA guidelines recommend two-drug therapy for patients with stage 2 HTN, making answers A and D incorrect. This patient recently suffered from a myocardial infarction, and the ACC/AHA guidelines recommend both β-blockers and ACE inhibitors or ARBs for treatment of HTN in ischemic heart disease, making answer B correct. Answer C would be an appropriate alternative regimen if the patient were African American, but W.D. is white.

7. Answer: B

T.J.'s blood pressure falls into the stage 1 HTN category. Patients with stage 1 HTN should receive pharmacologic treatment in addition to lifestyle modifications, making answer A incorrect. Patients with stage 1 HTN should be started on a single drug regimen, making answer D incorrect. According to the ACC/AHA guidelines, patients without medical conditions that direct drug therapy choices can be initiated on ACE inhibitors, ARBs, thiazide diuretics, or calcium channel blockers. However, because this patient is African American and she does not have heart failure, CKD, or type 2 diabetes with albuminuria, her initial HTN regimen should include a calcium channel blocker or a thiazide diuretic because these agents are more effective at lowering BP than ACE inhibitors and ARBs. Therefore, answer C is incorrect and answer B is the best choice.

8. Answer: C

This patient falls into the patient management group of patients with diabetes and age 40-75 years. Because she has multiple ASCVD risk factors including smoking, low HDL-C, and HTN, this patient would benefit from high-intensity statin therapy (answer C). Answer B would be correct if M.M. did not have additional ASCVD risk factors. Low-intensity statins are not recommended for initial therapy for any patient in the 2018 ACC/AHA Cholesterol guidelines (answer A). This patient should receive maximally tolerated statin therapy and be assessed for response before the addition of ezetimibe (Answer D).

9. Answer: C

A high-intensity statin should provide a ≥50% reduction in LDL-C. Atorvastatin 40 mg is considered a high-intensity statin because it will lower LDL by more than 50% (Answer C is correct). Pravastatin 20 mg (Answer A) and lovastatin 20 mg (Answer B) are considered low-intensity statins because they will lower LDL by less than 30%. Rosuvastatin 10 mg will reduce LDL 30%–50%; therefore, it is considered a moderate-intensity statin (Answer D).

10. Answer: C

If fasting TG concentrations are 500 mg/dL or greater or LDL-C is greater than 190 mg/dL, patients should be assessed for potential secondary causes of their dyslipidemia. Secondary causes of elevated TG include high intake of carbohydrates, excessive alcohol intake, oral estrogens, glucocorticoids, protease inhibitors, sirolimus (Answer C), thiazides, anabolic steroids, raloxifene, β-blockers, nephrotic syndrome, CKD, lipodystrophies, poorly controlled DM, hypothyroidism, pregnancy, and obesity. Amiodarone (Answer A), biliary obstruction (Answer B), and saturated fats (Answer D) are all secondary causes of increased LDL-C.

11. Answer: A

After placement of a drug-eluting stent for acute coronary syndrome, a $P2Y_{12}$ inhibitor is indicated for 12 months in most patients (Answer A is correct). Answer B is incorrect because 6 months of dual antiplatelet therapy (DAPT) is only for patients at high risk of bleeding, and this patient has no indication of being at high risk of bleeding. No current data support DAPT indefinitely (Answer C is incorrect). Answer D is incorrect because the guidelines recommend DAPT for at least 12 months, not 18, in most patients.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

This patient has HF*r*EF (NYHA class III), probably secondary to her MI 4 months ago, and is not receiving optimal HF therapy with an ACE inhibitor and β-blocker, making Answer A incorrect. ACE inhibitors are considered the cornerstone of therapy for HF*r*EF because evidence shows that they slow the progression of HF and reduce symptoms, hospitalizations, and mortality in this patient population. ACE inhibitors should be initiated in all patients with HF*r*EF, unless there is a contraindication. This patient has no contraindications for using an ACE inhibitor; therefore, lisinopril should be initiated (Answer D). Digoxin is not indicated unless a patient is symptomatic on optimal HF therapy (Answer B). This patient is not symptomatic and is not receiving optimal therapy. Although the patient is NYHA class III, no rationale exists for adding spironolactone at this time because she is not receiving optimal HF therapy (Answer C).

2. Answer: C

This patient is taking the target dose of enalapril; further increases in the enalapril dose are unnecessary unless the patient is hypertensive (Answer B). Compared with lower doses, higher doses of ACE inhibitors do not provide an additional reduction in all-cause or CV mortality. Adding β-blocker therapy, initially at a low dose, together with ACE inhibitor therapy, is recommended for further reductions in morbidity and mortality and for slowing the progression of HF (Answer C). Digoxin is indicated only in symptomatic patients, despite optimal therapy, and this patient's pharmacotherapy has not been optimized, making Answers A and D incorrect.

3. Answer: A

This patient has HF*p*EF, which is caused by a problem with ventricular relaxation. The preferred therapy is either a β-blocker or a nondihydropyridine CCB, each of which slows the HR and permits the ventricle greater time to fill with blood. Diltiazem, a non-DHP CCB, would be appropriate to initiate in this patient. Nifedipine can cause reflex tachycardia, which potentiates diastolic dysfunction by reducing ventricular filling time; therefore, this drug should be discontinued (Answer A). Diuretics should be used cautiously because patients with diastolic dysfunction are often fluid-dependent (preload) for maximal ventricular filling. In addition, this patient has no symptoms of systemic congestion, suggesting a need for increased diuresis, making Answer B incorrect. Digoxin has no role in managing diastolic dysfunction (Answer C). Although ACE inhibitors are first-line therapy for HF*r*EF, they can be considered in HF*p*EF if further antihypertensive therapy is needed after the HR is decreased (Answer D).

4. Answer: D

This patient's CHA_2DS_2-VASc score is 4 (risk factors are HTN, PAD, and age greater than 75 years), making him a candidate for an oral anticoagulant, such as warfarin, because of his AF. Use of an oral anticoagulant will greatly decrease his risk of stroke from about 5% per year to about 1% per year. Because his HR is less than 110 beats/minute with atenolol therapy, there is no reason to discontinue atenolol. In addition, there is reason to add an additional rate control drug, such as digoxin (Answer B) or diltiazem (Answer A). With his PAD, atorvastatin therapy is necessary, making Answer C incorrect. In addition, his BP is well controlled; therefore, increasing the lisinopril dose is not warranted, making Answer B incorrect. To derive the beneficial antiplatelet effects for CV event prevention, aspirin 81 mg is adequate. Aspirin 325 mg/day is also effective, but has a greater risk of bleeding with concomitant warfarin. Therefore, adding warfarin and decreasing the dose of aspirin to 81 mg/day (Answer D) is correct. This patient may also be a candidate for DOAC therapy over warfarin after checking renal function.

5. Answer: A

This patient is experiencing a rapid ventricular response with exercise or strenuous activity, causing the sensation of palpitations and dyspnea. Digoxin alone poorly controls the ventricular rate during times of high sympathetic influence (e.g., exercise). Additional therapy is usually necessary to control the ventricular rate adequately. A β-blocker such as metoprolol succinate is a good choice to maintain HR during activity (Answer A). Using verapamil with digoxin in this patient could result in signs or symptoms of toxicity, given his current digoxin concentration. In addition, he is already taking a CCB, making verapamil a bad choice (Answer D). Similarly, doubling the digoxin dose would almost double the current serum concentration to 2.2 ng/dL,

which should be avoided (Answer B). Instructing the patient to avoid activity is undesirable because physical activity should be encouraged and supported in all patients, especially in those with risk factors for CV disease (Answer C).

6. Answer: A
According to the ACC/AHA guidelines, this patient's BP goal is less than 130/80 mm Hg because he has no clinical CVD and a 10-year ASCVD risk ≥10%, making answers B and D incorrect. Beta blockers are not recommended first-line for HTN management in the absence of coronary artery disease, heart failure, or atrial fibrillation, making answer C incorrect. Answer A includes a first-line HTN medication which also maintains efficacy in the African American population.

7. Answer: D
This patient has been identified as being at risk of ASCVD, according to his pooled cohort equation result of 14.6%. Therefore, the patient falls into one of the four patient management groups (age 40–75 years with an LDL-C of 70–189 mg/dL and a 10-year ASCVD risk of 7.5-19.9% without DM or ASCVD) and thus should be initiated on statin therapy. According to the guidelines, this patient should be treated with moderate- to high-intensity statin therapy. Although simvastatin 20 mg is considered a moderate-intensity dose, adding gemfibrozil to this patient's regimen would be inappropriate because gemfibrozil is contraindicated in combination with simvastatin; also, his TG concentrations are less than 500 mg/dL and need not be specifically targeted (Answer A). Using pravastatin 20 mg would be inappropriate because this is considered a low-intensity dose, and it would not provide the more than 30%–50% reduction in LDL-C that is recommended. In addition, fenofibrate would not be needed because his TG concentrations are lower than 500 mg/dL (Answer C). Rosuvastatin 2.5 mg is a low-intensity dose and would not be appropriate (Answer B). Atorvastatin 20 mg is considered a moderate-intensity dose, and it will provide a 30%-50% reduction in LDL-C, as is recommended (Answer D).

8. Answer: D
This patient has a calculated 10-year ASCVD risk of 3.9%; therefore, he does not fall into one of the patient management groups. Thus, statin therapy at any intensity, moderate (Answer C) or high (Answer A), would be inappropriate. According to the cholesterol guidelines, patients who are 40–75 years old, without ASCVD or DM, and have an LDL-C of 70–189 mg/dL should have their 10-year risk score recalculated every 4–6 years, making Answer D correct and Answer B incorrect.

9. Answer: D
Secondary causes of hypertriglyceridemia should be ruled out when TG concentrations are greater than 500 mg/dL or when LDL-C is greater than 190 mg/dL. Different medications, conditions, and diet can affect these lipid values. Although obesity, poorly controlled DM, olanzapine, and metoprolol can increase TG concentrations, coenzyme Q does not affect TG; therefore, Answer A is incorrect. Alcohol consumption, poorly controlled DM, and β-blockers can all increase TG, but weight loss does not increase TG. Weight loss can actually lower LDL-C and TG; therefore, Answer B is incorrect. Although obesity and alcohol consumption can elevate TG, neither CCBs nor hyperthyroidism are expected to have this effect (Answer C is incorrect). All the conditions, medications, or disease states in Answer D can increase TG, making this option correct.

10. Answer: D
Oral contraceptives, specifically estrogen, can increase BP, especially with a longer duration of use. An alternative contraceptive without estrogen would be less likely to contribute to her HTN (Answer D is correct). Answers A and B are incorrect because her BP requires better control, but weight loss is unlikely to help because her BMI is normal. Answer C is incorrect because hydrochlorothiazide is no more potent than chlorthalidone.

11. Answer: B
ACE inhibitor therapy is contraindicated in pregnancy, and discontinuing ramipril is the most important next step, making Answers A and C incorrect. Answer D is incorrect because this patient will require good BP control during her pregnancy. Labetalol is a good choice of therapy because it is a preferred antihypertensive drug in pregnancy (Answer B is correct).

12. Answer: D
Because the patient has CHD, his options for antiarrhythmic therapy are limited. Class Ic antiarrhythmic drugs are contraindicated in patients with CHD; therefore, flecainide and propafenone cannot be used

(Answers B and C are incorrect). Disopyramide, a class Ia antiarrhythmic, is not a preferred therapy for AF; therefore, Answer A is incorrect. Sotalol, a class III antiarrhythmic, can be used in patients with CHD and good renal function; therefore, Answer D is correct.

Acute Care in Cardiology

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Learning Objectives

1. Distinguish between the treatments for acute coronary syndrome: ST-segment elevation myocardial infarction and non–ST-segment elevation acute coronary syndrome.
2. Formulate evidence-based treatment strategies for patients with acute decompensated heart failure.
3. Devise a treatment plan for patients presenting with ventricular or life-threatening arrhythmias.
4. Differentiate between goals and treatment for hypertensive emergencies and hypertension without progressive organ damage.

Abbreviations in This Chapter

AAD	Antiarrhythmic drug
ACE	Angiotensin-converting enzyme
ACLS	Advanced cardiac life support
ACS	Acute coronary syndrome
ACT	Activated clotting time
ADHF	Acute decompensated heart failure
ADR	Adverse drug reaction
AF	Atrial fibrillation
aPTT	Activated partial thromboplastin time
BNP	B-type natriuretic peptide
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CO	Cardiac output
CV	Cardiovascular
DAPT	Dual antiplatelet therapy
ECG	Electrocardiogram
EF	Ejection fraction
GI	Gastrointestinal
GP	Glycoprotein
GRACE	Global Registry of Acute Coronary Events
HF	Heart failure
HIT	Heparin-induced thrombocytopenia
ICD	Implantable cardioverter-defibrillator
LD	Loading dose
LOE	Level of evidence
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MI	Myocardial infarction
NSTE-ACS	Non–ST-segment elevation acute coronary syndrome
NSTEMI	Non–ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
PCWP	Pulmonary capillary wedge pressure
SCD	Sudden cardiac death
SHD	Structural heart disease
STEMI	ST-segment elevation myocardial infarction
SVR	Systemic vascular resistance
SVT	Supraventricular tachycardia
UA	Unstable angina
UFH	Unfractionated heparin
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 62-year-old man presents to the emergency department (ED) with the chief concern of chest pain that woke him from sleep and radiates to his jaw. An electrocardiogram (ECG) reveals ST-segment depression in leads II, III, and aVF. His blood pressure is 112/62 mm Hg and heart rate is 60 beats/minute. Cardiac enzymes have been obtained, and the first troponin result was slightly positive. Preparations are under way to take the patient to the cardiac catheterization laboratory for evaluation. Which medication regimen is most appropriate for this patient at this time?
   A. Aspirin 325 mg, clopidogrel 600-mg loading dose (LD), and unfractionated heparin (UFH) infusion 80-unit/kg bolus, followed by 18 units/kg/hour and metoprolol 5 mg intravenously.
   B. Aspirin 81 mg; prasugrel 60-mg LD; UFH infusion 60-unit/kg bolus, followed by 12 units/kg/hour; and intravenous enalaprilat.
   C. Aspirin 325 mg, ticagrelor 180-mg LD, and UFH infusion 60-unit/kg bolus, followed by 12 units/kg/hour.
   D. Aspirin 81 mg, prasugrel 60-mg LD, nitroglycerin infusion at 10 mcg/minute, and bivalirudin 0.75-mg/kg bolus and 1.75-mg/kg/hour infusion.

2. An 81-year-old African American man (weight 90 kg) presents to the ED with chest pressure (10/10 on a pain scale). His ECG reveals ST-segment depression in the inferior leads. His medical history is significant for hypertension and chronic kidney disease. Pertinent laboratory results are troponin 5.8 ng/L, serum creatinine (SCr) 3.7 mg/dL, and estimated creatinine clearance (eCrCl) 20 mL/minute. The patient has been given aspirin 325 mg single dose; a nitroglycerin drip, initiated at 5 mcg/minute, will be titrated to chest pain relief and blood pressure. The patient consents for cardiac catheterization after adequate hydration. Which anticoagulation strategy is most appropriate to initiate in this patient?
   A. Intravenous heparin 4000-unit intravenous bolus, followed by a 1000-unit/hour continuous infusion.
   B. Enoxaparin 90 mg subcutaneously every 12 hours.
   C. Fondaparinux 2.5 mg subcutaneously daily.
   D. Bivalirudin 67.5-mg bolus, followed by a 157-mg/hour infusion.

3. A 56-year-old man presents to the hospital with the chief concern of chest pain that was unrelieved at home with sublingual nitroglycerin. His ECG reveals ST-segment depression and T-wave inversion. Cardiac markers show an elevated troponin I. The cardiologist has requested that the patient go to the cardiac catheterization laboratory for further evaluation. The patient has a history of coronary artery disease (CAD) and had a myocardial infarction (MI) about 6 months ago. During his previous hospitalization, he was confirmed to have developed heparin-induced thrombocytopenia (HIT) after his platelet count (Plt) dropped to 40,000/mm^3 and he had a positive ELISA (enzyme-linked immunosorbent assay) upon serologic testing after his previous catheterization. Given this patient's diagnosis and history, which treatment regimen would be most appropriate during his cardiac catheterization?
   A. Abciximab.
   B. Bivalirudin.
   C. Enoxaparin.
   D. Tenecteplase.

4. A 62-year-old man presents to the ED after several hours of chest discomfort. His ECG reveals a 1- to 2-mm ST-segment elevation with positive troponins. He has also had increasing shortness of breath and lower-extremity swelling over the past 2–3 weeks. His medical history is significant for tobacco use for 40 years, chronic obstructive pulmonary disease, diabetes, and hypertension. His blood pressure is 102/76 mm Hg and heart rate is 111 beats/minute. He has rales in both lungs and 2–3+ pitting edema in his extremities. His echocardiogram reveals an ejection fraction (EF) of 25%. After primary percutaneous coronary intervention (PCI), he is transferred to the cardiac intensive care unit. Which best describes the acute use of β-blocker therapy in this patient?
   A. Give 12.5 mg of oral carvedilol within the first 24 hours.
   B. Give 5 mg of intravenous metoprolol at the bedside.
   C. Give 50 mg of oral metoprolol succinate at discharge.
   D. Give no β-blocker at this time.

5. A 60-year-old man (weight 75 kg) presents to the ED with crushing substernal chest pain and ST-segment elevations on ECG. He has a medical history of diabetes and a 40 pack-year history of smoking. He is taken immediately to the catheterization laboratory for primary PCI, and a drug-eluting stent is placed in his left anterior descending artery. In addition to aspirin, which regimen would best maintain this patient's stent patency?
   A. Clopidogrel 300-mg LD, followed by 75 mg daily for 12 months.
   B. Prasugrel 60-mg LD, followed by 10 mg daily for 12 months.
   C. Ticagrelor 180-mg LD, followed by 90 mg daily for 6 months.
   D. Clopidogrel 600-mg LD, followed by 75 mg daily for 6 months.

6. A 60-year-old woman with New York Heart Association (NYHA) class IV heart failure (HF) (heart failure with reduced ejection fraction [HFrEF]) is admitted for increased shortness of breath and dyspnea at rest. Her extremities appear

well perfused, but she has 3+ pitting edema in her lower extremities. Her vital signs include blood pressure 125/70 mm Hg, heart rate 92 beats/minute, and oxygen saturation (Sao_2) 89% on 100% facemask. After initiating an intravenous diuretic, which intravenous agent is best to rapidly treat this patient's pulmonary symptoms?

A. Dobutamine.
B. Milrinone.
C. Nitroglycerin.
D. Metoprolol.

7. A 75-year-old woman admitted for pneumonia has a history of NYHA class III HFrEF (left ventricular ejection fraction [LVEF] 25%) and several non–ST-segment elevation myocardial infarctions (NSTEMIs). She had an episode of sustained ventricular tachycardia (VT) during this hospitalization. Her corrected QT (QTc) interval was 380 milliseconds on the telemetry monitor, and her serum potassium and magnesium were 4.6 mEq/L and 2.2 mg/dL, respectively. Which intravenous agent is most appropriate for this patient's ventricular arrhythmias?

A. Procainamide.
B. Metoprolol.
C. Magnesium.
D. Amiodarone.

8. A 53-year-old woman is admitted to the hospital after the worst headache she has ever had. Her medical history includes exertional asthma, poorly controlled hypertension, glaucoma, and hyperlipidemia. She is nonadherent to her medications and has not taken her prescribed blood pressure medications for 4 days. Vital signs include blood pressure 220/100 mm Hg and heart rate 65 beats/minute. She has retinal hemorrhaging on funduscopic examination. Which is most appropriate for this patient's hypertensive emergency?

A. Fenoldopam 0.1 mcg/kg/minute.
B. Nicardipine 5 mg/hour.
C. Labetalol 0.5 mg/minute.
D. Enalaprilat 0.625 mg intravenously every 6 hours.

9. A 52-year-old woman has a witnessed cardiac arrest in a shopping mall and is resuscitated with an automatic external defibrillator device. On electrophysiologic study, she has inducible VT. Which is most appropriate for reducing the secondary incidence of sudden cardiac death (SCD)?

A. Propafenone.
B. Amiodarone.
C. Implantable cardioverter-defibrillator (ICD).
D. Metoprolol.

10. The Sudden Cardiac Death in Heart Failure trial evaluated the efficacy of amiodarone or an ICD versus placebo in preventing all-cause mortality in ischemic and nonischemic patients with NYHA class II and III HF. There was a 7.2% absolute risk reduction and a 23% relative risk reduction in all-cause mortality at 60 months with an ICD versus placebo. Which best shows the number of patients needed to treat with an ICD to prevent one death versus placebo?

A. 1.
B. 4.
C. 14.
D. 43.

11. You are working on a review article about newer treatment strategies for hypertensive crises. You want to ensure that you retrieve all relevant clinical trials and related articles on your subject. Which comprehensive database is most appropriate to search to ensure that you have not missed key articles?

A. International Pharmaceutical Abstracts.
B. Iowa Drug Information Service.
C. Clin-Alert.
D. Excerpta Medica.

12. A physician on your team asks that you report an adverse drug reaction (ADR) experienced by a patient taking nesiritide. The patient had severe hypotension after the initial bolus dose of nesiritide, though his blood pressure was in the normal range before therapy initiation. The hypotension led to reduced renal perfusion, resulting in oliguric

acute kidney injury and subsequent hemodialysis. The patient had no known renal insufficiency before developing this complication. Which statement best describes The Joint Commission requirements for institutional ADR reporting?

A. A MedWatch form must be completed that explains the situation in which the ADR occurred.

B. Institutions must create their own definition of ADR with which practitioners will be familiar.

C. Hospital staff members must use the Naranjo algorithm to assess the severity of the ADR.

D. Only severe or life-threatening ADRs need to be reported.

13. Your pharmacy and therapeutics committee wants you to do a pharmacoeconomic analysis of a new drug available to treat decompensated HF. This drug has a unique mechanism of action. Unlike other available inotropic therapies that can increase mortality, this drug appears to reduce long-term mortality. However, its cost is 10-fold greater than other available drugs. Which pharmacoeconomic analysis would best determine whether this new drug is a better formulary choice than the currently available agents?

A. Cost-minimization.

B. Cost-effectiveness.

C. Cost-benefit.

D. Cost-utility.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient–centered pharmacotherapy
    a. Tasks 1:1–17, 2:1–5, 7, 3:1–5, 4:1–7, 5:1–5
    b. Systems and patient-care problems:
        i. Acute coronary syndrome
        ii. Acute decompensated heart failure
        iii. Adult cardiac arrest
        iv. Advanced cardiac life support
        v. Basic life support and cardiopulmonary resuscitation
        vi. Life-threatening arrhythmias
        vii. Hypertensive crises (urgency and emergency)
2. Domain 2: Drug Information and Evidence-Based Medicine, Tasks 1:2, 3, 2:1, 5, 6, and 3:1, 2
3. Domain 3: System-Based Standards and Population-Based Pharmacotherapy, Tasks 1:4

I. ACUTE CORONARY SYNDROME

A. Definitions
1. Acute coronary syndrome (ACS) is a spectrum of conditions compatible with acute myocardial ischemia or infarction caused by an abrupt reduction in coronary blood flow (Figure 1).
2. This chapter will focus on the most common presentation of ACS (type 1 MI), as defined by the Fourth Universal Definition of Myocardial Infarction, which is caused by coronary thrombosis.
3 Atherogenic plaque rupture is the underlying pathophysiology for ACS, causing several prothrombotic substances to be released, which results in platelet activation and aggregation and eventual thrombus formation leading to partial or total occlusion of the coronary artery.
4. ACS can be divided into ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation acute coronary syndrome (NSTE-ACS).
   a. STEMI
      i. Defined by characteristic symptoms of myocardial ischemia in association with persistent ST-segment elevation on ECG with positive troponins
      ii. STEMI is an indication for immediate coronary angiography to determine whether reperfusion can be done (see section C in this section, "Decision for Invasive Management").
   b. NSTE-ACS
      i. Suggested by the absence of persistent ST-segment elevation on ECG
      ii. NSTE-ACS can be divided into unstable angina (UA) and NSTEMI according to whether cardiac biomarkers of necrosis are present. UA and NSTEMI are closely related conditions whose pathogenesis and clinical presentation are similar but vary in risk and severity.
      iii. ECG abnormalities and elevated troponins in isolation are insufficient to make the diagnosis and must be interpreted in the appropriate clinical context (Table 1).
      iv. Optimal inhibition of thrombosis is paramount in ACS management.

B. Clinical Assessment and Initial Evaluation
1. A 12-lead ECG should be done and interpreted within 10 minutes of presentation.
   a. Persistent ST-segment elevation should be treated according to the STEMI guidelines.
   b. Serial ECGs can be done if the initial ECG is nondiagnostic.
2. Serial cardiac troponins should be obtained at presentation and 3–6 hours after symptom onset.
3. At initial presentation, the clinical history, angina symptoms and equivalents, physical assessment, ECG, renal function, and cardiac troponin measurements can be integrated into an estimation of the risk of death and nonfatal cardiac ischemic events, which is useful for selecting the site of care, antithrombotic therapies, and invasive management. Risk calculators include the following:
   a. Thrombolysis in myocardial infarction (TIMI) risk score (available at www.timi.org [accessed September 1, 2018]) is useful in predicting 30-day and 1-year mortality in patients with NSTE-ACS.
      i. Composed of seven 1-point indicators rated on presentation; 1 point is given for each of the following: 65 or older, three or more risk factors for CAD, prior coronary stenosis 50% or greater, ST deviation on ECG, two or more anginal events in previous 24 hours, aspirin use in previous 7 days, and elevated cardiac biomarkers
      ii. Risk of mortality, new or recurrent MI, or severe recurrent ischemia through 14 days; 0–2 is low risk, 3 is intermediate risk, and 4 or more is high risk
      iii. Patients with higher risk scores (e.g., TIMI of 3 or more) have a greater benefit from therapies such as low-molecular-weight heparin, glycoprotein (GP) IIb/IIIa inhibitors, and invasive strategies.
   b. The Global Registry of Acute Coronary Events (GRACE) risk model (www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html [accessed September 1, 2018]) predicts in-hospital and postdischarge mortality or MI. Patients with high GRACE risk model scores (i.e., GRACE score greater than 140) can be identified for early invasive strategies.

Table 1. ACS Definition

	Subjective Findings	Objective Findings	Extent of Injury
NSTE-ACS UA	Most commonly presents as a pressure-type chest pain that typically occurs at rest or with minimal exertion Pain usually starts in the retrosternal area and can radiate to either or both arms, neck, or jaw Pain may also present with diaphoresis, dyspnea, nausea, abdominal pain, or syncope Unexplained new-onset or increased exertional dyspnea is the most common angina equivalent Less common atypical symptoms[a] (without chest pain) include epigastric pain, indigestion, nausea, vomiting, diaphoresis, unexplained fatigue, and syncope	ST-segment depression, T-wave inversion, or transient or nonspecific ECG changes can occur No positive biomarkers for cardiac necrosis	No myocardial injury; partial occlusion of coronary artery
NSTEMI		ST-segment depression, T-wave inversion, or transient or nonspecific ECG changes can occur Positive biomarkers (troponin I or T elevation)	Myocardial injury; partial occlusion of coronary artery
STEMI	Classic symptoms include worsening of pain or pressure in chest, characterized as viselike, suffocating, squeezing, aching, gripping, and excruciating, that may be accompanied by radiation	ST-segment elevation > 1 mm above baseline on ECG in two or more contiguous leads Positive biomarkers (troponin I or T elevation)	Myocardial necrosis; total occlusion of coronary artery

[a]Up to one-half of all MIs are silent or unrecognized, and one-third present with symptoms other than chest discomfort.

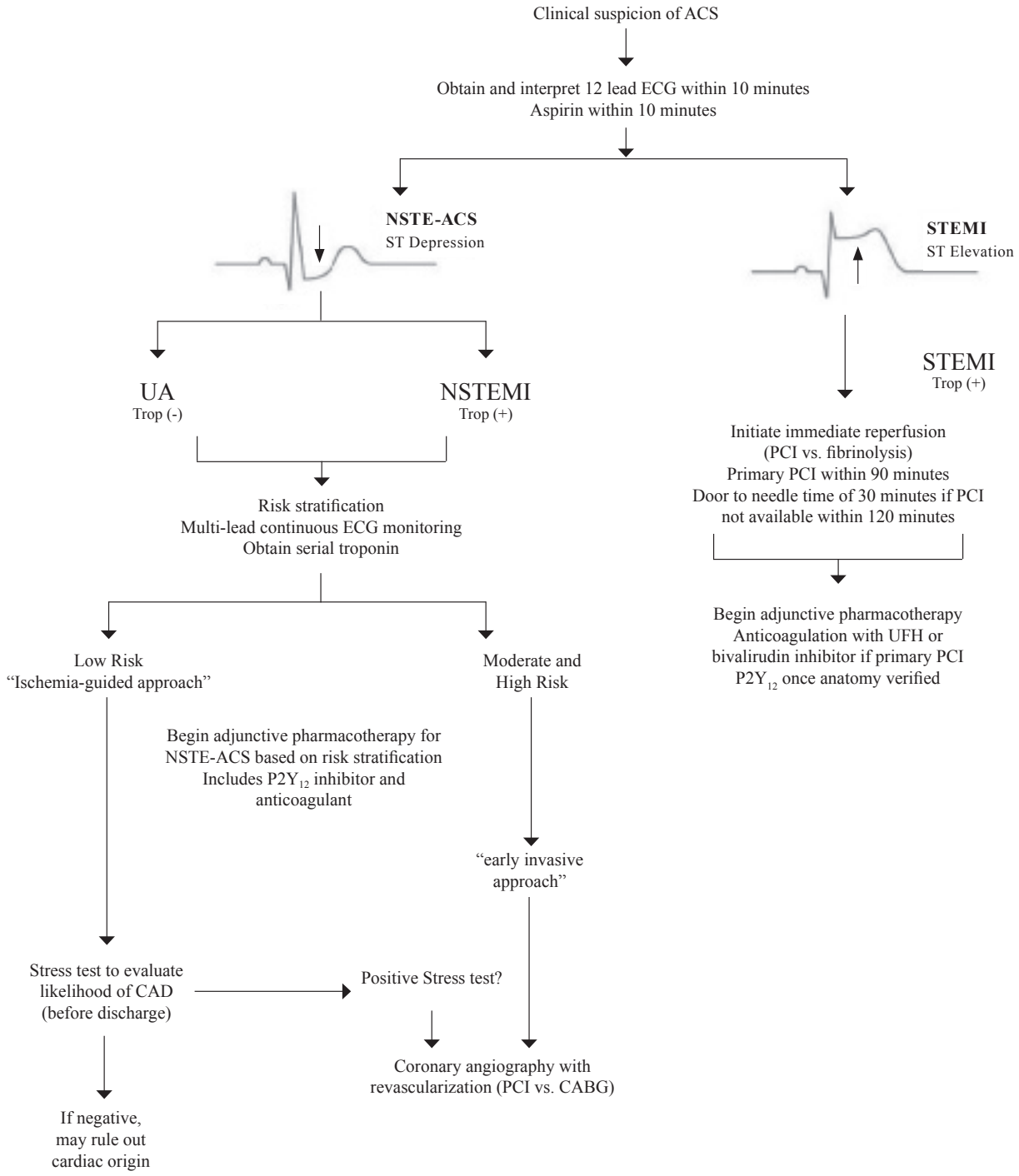

Figure 1. Acute coronary syndrome diagnosis and risk stratification.

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CAD = coronary artery disease; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina; UFH = unfractionated heparin.

C. Decision for Invasive Management
   1. STEMI
      a. The goal of therapy is to restore the patency of the infarct-related artery and minimize the infarct size. Secondary goals include preventing complications such as arrhythmias or death as well as controlling chest pain and associated symptoms.
      b. Requires urgent revascularization either interventionally or with drug therapy (i.e., fibrinolysis)
      c. Primary PCI is preferred to lytic therapy. Performance measure includes goal of primary PCI within 90 minutes of first medical contact.
      d. Fibrinolytic therapy is indicated for patients with a STEMI in whom PCI cannot be done (discussed later in chapter). If PCI cannot be done within 120 minutes, performance measure for lytic administration includes a door-to-needle time of 30 minutes.
   2. NSTE-ACS
      a. The goal of therapy is to prevent total occlusion of the related artery and to control chest pain and associated symptoms. Patients with NSTE-ACS are treated on the basis of risk (TIMI, GRACE) with either an early invasive strategy (interventional approach) or an ischemia-guided strategy (a conservative management strategy using medications rather than an interventional approach).
      b. Early invasive strategy is a diagnostic angiography with intent to do revascularization, if appropriate, depending on coronary anatomy.
         i. Indicated in those with NSTE-ACS who have refractory angina or hemodynamic or electrical instability or those with high risk on the basis of clinical findings
         ii. Routine invasive therapy is generally superior to an ischemia-guided strategy (results in lower rates of recurrent UA, recurrent hospitalization, MI, and death) in patients with one or more of the following risk features: advanced age (older than 70), previous MI or revascularization, ST deviation, HF, depressed resting left ventricle (LV) function (i.e., LVEF less than 40%), noninvasive stress findings, high TIMI or GRACE scores, markedly elevated troponins, and diabetes.
         iii. Not for those with serious comorbidities or contraindications to such procedures (hepatic, renal, pulmonary failure, cancer), for whom the risks for the procedure may outweigh the benefits of revascularization
      c. Ischemia-guided therapy seeks to avoid the routine early use of invasive procedures unless patients have refractory or recurrent ischemic symptoms or develop hemodynamic instability.
         i. Recommended for patients with a low risk score (TIMI 0 or 1, GRACE less than 109)
         ii. Indicated for those with acute chest pain with a low likelihood of ACS who are troponin negative (preferred for low-risk women)
         iii. Can be chosen according to clinician and patient preference
   3. Patients should receive anti-ischemic and analgesic medications early in care: morphine, oxygen, nitroglycerin, and aspirin plus a β-blocker (Table 2).

Table 2. Initial Anti-ischemic and Analgesic Therapies for ACS

Therapy	Comments
M = Morphine or other narcotic analgesic	Provides analgesia and decreased pain-induced sympathetic/adrenergic tone Commonly used because it can also induce vasodilation and mediate some degree of preload and afterload reduction Morphine 1–5 mg IV every 5–30 min is reasonable if symptoms are not relieved despite maximally tolerated anti-ischemic medications[a] Carries a class IIb recommendation, given that at least two large trials have identified an association between morphine administration and risk of death[b] Slows the absorption of antiplatelet therapy, reduces time to peak antiplatelet activity, and may decrease area under the curve
O = Oxygen	Can help attenuate anginal pain secondary to tissue hypoxia Consider supplemental oxygen if Sa_{O_2} < 90%, respiratory distress, or high-risk features of hypoxemia[c] Excessive supplemental oxygen without depressed SaO_2 can be associated with increased morbidity and mortality
N = Nitroglycerin	Facilitates coronary vasodilation and may also be helpful in severe cardiogenic pulmonary edema caused by venous capacitance NTG spray or sublingual tablet (0.3–0.4 mg) every 5 min for up to three doses to relieve acute chest pain (if pain is unrelieved after one dose, call 9-1-1); afterward, assess need for IV administration IV administration used in first 48 hr for persistent ischemic chest pain, HF, and HTN IV NTG 5–10 mcg/min; titrate to chest pain relief or max 200 mcg/min Use should not preclude other mortality-reducing therapies (β-blocker, ACE inhibitor) Contraindications: Sildenafil or vardenafil (use within 24 hr) or tadalafil (use within 48 hr); SBP < 90 mm Hg or ≥ 30 mm Hg below baseline, HR < 50 beats/min, HR > 100 beats/min in absence of symptomatic HF; right ventricular infarction
A = Aspirin	Inhibits platelet activation Mortality-reducing therapy Chew and swallow non–enteric coated aspirin 162–325 mg × 1 dose[c] Clopidogrel if aspirin allergy Performance measure
β-Blocker	Decrease myocardial ischemia, reinfarction, and frequency of dysrhythmias and increase long-term survival Oral β-blocker[c] should be initiated within 24 hr in patients who do not have signs of HF, evidence of low-output state, increased risk of cardiogenic shock, or other contraindications to β-blockade (e.g., PR interval > 0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease) Reasonable to continue in patients with NSTE-ACS with normal LV function[a] Use metoprolol succinate, carvedilol, or bisoprolol in concomitant stabilized HFrEF[c]; add cautiously in decompensated HF Avoid agents with intrinsic sympathomimetic activity (acebutolol, pindolol, penbutolol) IV β-blocker[d] is potentially harmful in patients with risk factors for shock (age > 70 yr, HR > 110 beats/min, SBP < 120 mm Hg, and late presentation)

[a]Class IIb may be considered.

[b]From: Montalescot G, van't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med 2014;371:1016-27; and Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J 2005;149:1043-9.

[c]Class I = should be performed or administered; class IIa = reasonable to be performed or administered.

[d]Class III = not to be administered or harmful.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; HTN = hypertension; LV = left ventricle; NTG = nitroglycerin; SBP = systolic blood pressure.

4. Patients with STEMI and NSTE-ACS should be treated with antiplatelet and anticoagulant therapy (Tables 3–9).
   a. Platelets are activated by several different mechanisms, only some of which can be inhibited by medications.
   b. Combination therapy with several antiplatelet agents plus a concomitant anticoagulant is the mainstay of acute ACS management, which targets the underlying pathophysiology of thrombus formation in ACS.
   c. The roles and combinations of antiplatelet therapies continue to be refined through clinical trials in varying subsets of ACS presentation (Table 3).
   d. In general, all patients receive aspirin and $P2Y_{12}$ receptor antagonists, and a minority of patients may benefit from the addition of GP IIb/IIIa inhibition in the acute management of ACS.

Table 3. Antiplatelet Management Strategies According to ACS Presentation

Antiplatelet Agent	NSTE-ACS Ischemia Guided	NSTE-ACS Invasive	STEMI Primary PCI	STEMI + Fibrinolytic
Aspirin	Aspirin	Aspirin	Aspirin	Aspirin
$P2Y_{12}$ receptor antagonist	Clopidogrel TIC	Clopidogrel PRA[a] TIC[a]	Clopidogrel PRA TIC	Clopidogrel[b]
GP IIb/IIIa inhibitor	Greatest benefit when given to patients with high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or TIC[c]			

[a]It may be reasonable to choose TIC or PRA (in those who are not at high bleeding risk) over clopidogrel in patients treated with early invasive strategy for NSTE-ACS (class IIa, 2014 NSTE-ACS guideline).

[b]Pre-PCI after fibrinolytic therapy: 300-mg LD if within 24 hr of event; clopidogrel 600-mg LD if > 24 hr after event.

[c]Benefit from adding GP IIb/IIIa inhibitors to aspirin therapy is greatest among those with highest-risk features (those with elevated biomarkers, those with diabetes, those undergoing revascularization) and in those not receiving adequate pretreatment with $P2Y_{12}$ inhibitor. It is reasonable (class IIa, 2014 NSTE-ACS guideline) to give GP IIb/IIIa inhibitors to high-risk patients with NSTE-ACS treated with UFH and adequately pretreated with clopidogrel.

PCI = percutaneous coronary intervention; PRA = prasugrel; TIC = ticagrelor.

   e. Antiplatelet recommendations
      i. Aspirin
         (a) An irreversible cyclooxygenase-1 inhibitor blocking the formation of thromboxane A_2– and thromboxane A_2–mediated platelet activation
         (b) Given to all patients (class I)
         (c) Established first-line therapy in ACS; reduces the incidence of recurrent MI and death
         (d) LD is necessary for aspirin-naive patients; avoid enteric coated initially because of delayed and reduced absorption.
            (1) Dosing is 162–325 mg for patients at initial presentation of ACS (Table 4).
            (2) Dosing is 81–325 mg for those who are undergoing PCI, depending on chronic aspirin therapy regimen.
         (e) Aspirin is given indefinitely at a preferred dose of 81 mg after ACS with or without PCI (class I).
            (1) High dose (greater than 160 mg) is associated with more bleeding than lower dose (less than 160 mg).
            (2) High doses (greater than 160 mg) have not been shown to improve outcomes after ACS more effectively than lower doses (less than 160 mg).

(f) Dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ receptor inhibitor is indicated for all patients after ACS for at least 12 months (see D, "Long-term Management After ACS"). The optimal aspirin dose in patients treated with DAPT appears to be 75–100 mg daily.

Table 4. Guideline Recommendations for Aspirin Therapy in ACS with or without PCI[a]

Guideline Recommendation	Class/Grade
Initiate 162–325 mg of ASA before PCI; after PCI, give ASA indefinitely • 2013 ACCF/AHA guideline for STEMI	I
Initiate 81–325 mg of non–enteric-coated ASA before PCI in patients already taking ASA; in patients not taking ASA, give 325 before PCI; after PCI, continue ASA indefinitely • 2014 NSTE-ACS guideline • 2011 ACCF/AHA/SCAI guideline for PCI	I
81 mg of ASA preferred to higher maintenance doses • 2014 NSTE-ACS guideline • 2013 ACCF/AHA guideline for STEMI • 2011 ACCF/AHA/SCAI guideline for PCI	IIa IIa IIa

[a]Class I = should be performed or administered; class IIa = reasonable to be performed or administered; class IIb = may be considered; class III = not to be administered or harmful.

ACCF = American College of Cardiology Foundation; AHA = American Heart Association; ASA = acetylsalicylic acid; SCAI = Society for Cardiovascular Angiography and Interventions.

ii. $P2Y_{12}$ inhibitors
   (a) Inhibit the effect of adenosine diphosphate on the platelet, a key mediator resulting in amplification of platelet activation
   (b) $P2Y_{12}$ inhibitor therapy is given to all patients (class I).
   (c) Choice of oral $P2Y_{12}$ inhibitor depends on an ischemia-guided therapy or early invasive approach and pharmacokinetic differences (Tables 5–7).
      (1) Prasugrel should not be administered to patients with a history of stroke or transient ischemic attack (class III).
      (2) The efficacy of ticagrelor is decreased in patients treated with higher doses of aspirin (greater than 300 mg daily) compared with lower doses (less than 100 mg daily).
   (d) Clopidogrel and ticagrelor are preferred for a medical (i.e., ischemia-guided) strategy (Table 5).
   (e) Clopidogrel, ticagrelor, and prasugrel are options for an early invasive strategy (Table 5).
      (1) It is reasonable to choose ticagrelor over clopidogrel for $P2Y_{12}$ inhibition in patients with NSTE-ACS or STEMI treated with an early invasive strategy or coronary stenting (class IIa).
      (2) It is reasonable to choose prasugrel over clopidogrel for $P2Y_{12}$ inhibition in patients with NSTE-ACS or STEMI who undergo PCI and who are not at high risk of bleeding complications and have no history of transient ischemic attack or stroke (class IIa).
      (3) Although not yet included in guidelines, results of the first head-to-head ISAR-REACT 5 open-label trial showed that prasugrel was superior to ticagrelor in reducing ischemic end points (6.9% vs. 9.3%, p=0.0006) without increasing bleeding risk in 4018 patients with ACS undergoing PCI; however, limitations to this study have been identified.
   (f) Limited data are available on the long-term safety or efficacy of "switching" patients treated for weeks or months with a $P2Y_{12}$ inhibitor to a different $P2Y_{12}$ inhibitor.

Table 5. Guideline Recommendations for $P2Y_{12}$ Inhibitor Therapy in ACS with or without PCI

Guideline Recommendation	Class/Grade[a]
An LD of $P2Y_{12}$ receptor inhibitor should be given before PCI. Options include: a. Clopidogrel[b] 600 mg followed by 75 mg daily; b. PRA 60 mg followed by 10 mg daily; or c. TIC 180 mg followed by 90 mg BID • 2013 ACCF/AHA guideline for STEMI • 2014 NSTE-ACS guideline	I LOE B LOE B LOE B
For patients with NSTE-ACS treated with an early invasive or ischemia-guided strategy: a. Clopidogrel 600 mg followed by 75 mg daily b. TIC 180 mg followed by 90 mg BID • 2014 NSTE-ACS guideline	I LOE B LOE B
For patients with NSTE-ACS treated with an early invasive or ischemia-guided strategy: It is reasonable to use TIC in preference to clopidogrel • 2014 NSTE-ACS guideline	IIa LOE B
For patients with NSTE-ACS treated with PCI who are not at risk of bleeding complications: • It is reasonable to choose PRA over clopidogrel • 2014 NSTE-ACS guideline	IIa LOE B
PRA should not be administered to patients with a history of TIA or stroke • 2014 NSTE-ACS guideline • 2013 ACCF/AHA guideline for STEMI	Class III

[a]Class I = should be performed or administered; class IIa = reasonable to be performed or administered; class IIb = may be considered; class III = not to be administered or harmful.

[b]Before PCI after fibrinolytic therapy: 300-mg LD if within 24 hr of event; clopidogrel 600-mg LD if > 24 hr after event.

BID = twice daily; LOE = level of evidence; TIA = transient ischemic attack.

Table 6. Comparison of Oral $P2Y_{12}$ Receptor Inhibitors

Parameter	Clopidogrel (Plavix)[a]	Prasugrel (Effient)[b]	Ticagrelor (Brilinta)[c]
Mechanism of action	Thienopyridine; inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor	Thienopyridine; inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor	Inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor
Peak platelet inhibition	300-mg LD ~6 hr 600-mg LD ~2 hr	60-mg LD ~30 min[d]	180 mg LD ~30 min[d]
% Platelet inhibition	30%–40%	60%–70%	60%–70%
LD	300–600 mg[e]	60 mg	180 mg
Maintenance dose	75 mg daily	10 mg daily; (5 mg if < 60 kg, BW ≥ 75 yr)[f]	90 mg BID[g]
Metabolism	Prodrug; converted by two-step process to active metabolite involving 2C19 in addition to other CYP enzymes	Prodrug; converted by one step to active metabolite by several CYP pathways	Not prodrug; reversible, noncompetitive binding; 3A4 (primary), 3A5, P-gp inhibitor
Reversible platelet binding	No	No	Yes
Half-life	8 hr (metabolite)	3.7 hr (metabolite, range 2–15 hr)	7 hr (parent), 9 hr (active metabolite)
Nonresponders	Exposure to active drug affected by *CYP2C19* genetic polymorphisms	No known issues	No known issues

Table 6. Comparison of Oral $P2Y_{12}$ Receptor Inhibitors *(Cont'd)*

Parameter	Clopidogrel (Plavix)[a]	Prasugrel (Effient)[b]	Ticagrelor (Brilinta)[c]
Drug-drug interactions, drug-disease interactions, and common nonbleeding-related AEs	PPIs inhibit *CYP2C19* (concomitant use with esomeprazole/omeprazole is discouraged on package labeling); increased bleeding with NSAIDs, OACs, O3FAs	No clinically significant drug interactions; more bleeding with NSAIDs, OACs	Careful with asthma owing to dyspnea (up to 15%) and bradycardia (can cause ventricular pauses): More bleeding with NSAIDs, OACs Strong 3A4 inhibitors increase TIC concentrations; strong 3A4 inducers decrease TIC concentrations; do not exceed 40 mg of simvastatin or lovastatin Limit aspirin to < 100 mg; monitor digoxin concentrations
Surgery hold time[h]	5 days	7 days	5 days
Bleeding risk	Less than PRA and TIC with standard dosing	Risk of non-CABG, spontaneous, and fatal bleeds higher than with standard-dose clopidogrel	Risk of non-CABG bleeds higher than with standard-dose clopidogrel
Box warning	*CYP2C19* polymorphisms	Age-related bleeding; CVA/TIA	Aspirin dosing > 100 mg
Contraindications	Active bleeding	Active bleeding; TIA, CVA	Active bleeding; ICH; severe hepatic disease
Supporting trials	CREDO, CURE, PCI-CURE, CLARITY, COMMIT	TRITON-TIMI 38, TRILOGY	PLATO, PEGASUS
FDA indication	ACS managed medically or with PCI	ACS with PCI	ACS managed medically or with PCI

[a]Administer clopidogrel indefinitely if aspirin allergy. Avoid LD if patient is ≥ 75 yr in STEMI when fibrinolysis is given.

[b]Avoid PRA in patients with active pathologic bleeding or a history of TIA or CVA and in patients > 75 yr unless the patient has diabetes mellitus or a history of MI.

[c]Avoid TIC in patients with active pathologic bleeding or a history of ICH. Avoid aspirin doses > 100 mg daily (exception: first dose of 325 mg).

[d]A significant antiplatelet effect has been observed at 30 min. Onset of effect is quicker, and extent of platelet inhibition is greater than with clopidogrel.

[e]A 600-mg LD results in greater, more rapid, and more reliable platelet inhibition than a 300-mg LD.

[f]Although 5 mg in patients weighing < 60 kg should be considered, this dose has not been studied in patients undergoing PCI.

[g]Maintenance dosing of 60 mg BID is FDA approved for reducing thrombotic events after an initial 12 mo of therapy.

[h]In emergency CABG, clopidogrel and TIC should be held for at least 24 hr to minimize the risk of CABG-related bleeding.

ADP = adenosine diphosphate; AE = adverse event; BW = boxed warning; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; CYP = cytochrome P450; FDA = U.S. Food and Drug Administration; ICH = intracranial hemorrhage; NSAID = nonsteroidal anti-inflammatory drug; O3FA = omega-3 fatty acid; OAC = oral anticoagulant; P-gp = P-glycoprotein; PPI = proton pump inhibitor; TIA = transient ischemic attack.

ii. Intravenous $P2Y_{12}$ inhibitor
   (a) Cangrelor, a direct-acting, rapidly reversible, intravenous $P2Y_{12}$ inhibitor, achieves a high level of platelet inhibition (greater than 90% with a 30-mcg/kg intravenous bolus followed by a 4-mcg/kg/minute infusion) within 5 minutes and reaches steady state within 15–30 minutes of administration.
   (b) Rapid onset and offset (half-life less than 5 minutes) allows a quick, high degree of platelet inhibition with resolution of normal platelet function within 1 hour of ending treatment.
   (c) Primarily studied in the setting of PCI only and may be considered in those who are not candidates for oral agents

(d) Pivotal trials comparing cangrelor with clopidogrel in ACS have not shown the superiority of cangrelor; however, both the CHAMPION PHOENIX PCI and the PLATFORM trials were discontinued prematurely.
(e) Cangrelor had better efficacy than post-PCI clopidogrel with increases in minor bleeding (not major) (CHAMPION PHOENIX).
(f) Cangrelor treatment is associated with a risk of dyspnea.
(g) Cangrelor has not been studied in settings with preloaded clopidogrel or compared with prasugrel or ticagrelor.
(h) Cangrelor has a potential use as a bridge therapy after discontinuation of oral $P2Y_{12}$ inhibitors in high-risk patients undergoing coronary artery bypass grafting (CABG) (JAMA 2012;307:265-74).
(i) The onset of action of both clopidogrel and prasugrel is delayed when coadministered with cangrelor, suggesting that cangrelor preferentially binds to the $P2Y_{12}$ and prevents irreversible inhibition with prasugrel and clopidogrel's active metabolite. Therefore, clopidogrel and prasugrel should not be initiated until termination of the cangrelor infusion. No such drug interaction exists with ticagrelor.
(j) Expense and lack of evidence showing superiority to other $P2Y_{12}$ inhibitors limit cangrelor's use.
(k) Cangrelor has not been included in the ACS guidelines to date because FDA approval occurred after guideline release.

iv. Intravenous GP IIb/IIIa inhibitors
(a) Intravenous GP IIb/IIIa receptor inhibitors can be added to aspirin with or without an oral $P2Y_{12}$ inhibitor for cardiovascular (CV) benefit in select high-risk patients in the acute management of ACS.
(b) Block the final common pathway of platelet aggregation; achieve 80% inhibition of ex vivo platelet aggregation
(c) GP IIb/IIIa inhibition may be beneficial in patients with high-risk features, particularly in those inadequately pretreated with $P2Y_{12}$ inhibition.
(d) Double-bolus eptifibatide and high-dose bolus tirofiban are class I options for the invasive strategy (Table 7).
(e) GP IIb/IIIa inhibitors reduce the incidence of composite ischemic events, primarily through decreasing documented MIs, but can increase the risk of bleeding.
(f) Most, but not all, data were gathered in the era before routine $P2Y_{12}$ inhibitor use.
(g) Benefit from adding GP IIb/IIIa inhibitors to aspirin therapy is greatest among those with highest-risk features (elevated biomarkers, diabetes, undergoing revascularization) and in those not receiving adequate pretreatment with clopidogrel or ticagrelor.
(h) It is reasonable (class IIa, 2014 NSTE-ACS guideline) to give GP IIb/IIIa inhibitors to high-risk patients with NSTE-ACS treated with UFH and adequately pretreated with clopidogrel or ticagrelor.
(i) Most studies combined GP IIb/IIIa inhibitors with UFH as the anticoagulant.
(j) Upstream administration (given before PCI) has not been shown superior to delayed administration (given at time of PCI).
(1) Upstream administration is noninferior to delayed timing for reducing ischemic events.
(2) Significantly higher bleeding rates occur in those receiving upstream GP IIb/IIIa inhibitors than in those receiving delayed administration.
(3) Bolus-only GP IIb/IIIa inhibitor administration has been adopted in clinical practice but not in the practice guidelines.

(k) Common adverse events of GP IIb/IIIa inhibitors:
  (1) Most common adverse effect is bleeding, with rates as low as 1.4% and as high as 10.6%, depending on length of therapy and how bleeding rates were accrued in the individual studies.
  (2) Note that the smaller-molecule agents eptifibatide and tirofiban depend on renal clearance; adjustment of the infusion is recommended to decrease the risk of bleeding; monitor SCr (CrCl).
  (3) All GP IIb/IIIa inhibitors can cause thrombocytopenia; monitor hemoglobin (Hgb), hematocrit (Hct), and Plt. When administered with UFH, rates of thrombocytopenia with either tirofiban or eptifibatide are no greater than with UFH alone.
  (4) Secondary to their short half-life, eptifibatide and tirofiban can be reversed within a few hours by discontinuing the infusion and are preferred (class IIb) in the NSTE-ACS guideline.

Table 7. GP IIb/IIIa Inhibitor Dosing in ACS with or without PCI[a,b]

Agent	Dosing	Renal Adjustments
Eptifibatide (Integrilin)	PCI: 180 mcg/kg IVB × 2 (10 min apart); 2 mcg/kg/min initiated after first bolus for 18–24 hr[c]; ACS without PCI: Of uncertain benefit in patients adequately pretreated with a $P2Y_{12}$ receptor inhibitor; single bolus used as above	If CrCl < 50 mL/min, reduce infusion by 50%; avoid in patients on hemodialysis; not studied in patients with SCr > 4 mg/dL
Tirofiban (Aggrastat)	PCI: 25 mcg/kg IVB over 3 min; then 0.15 mcg/kg/min for 18 hr	If CrCl ≤ 60 mL/min, reduce infusion by 50%

[a]Adding GP IIb/IIIa inhibitors to aspirin therapy is most beneficial in patients with high-risk features (those with elevated biomarkers, those with diabetes, those undergoing revascularization) and in those not receiving adequate pretreatment with $P2Y_{12}$ inhibitors. Administration of GP IIb/IIIa inhibitors to patients adequately treated with $P2Y_{12}$ inhibitors is of uncertain clinical benefit.

[b]GP IIb/IIIa inhibitors should be used in combination with heparin (either UFH or low-molecular-weight heparin) or used provisionally with bivalirudin and aspirin.

[c]Double bolus is recommended to support PCI in STEMI and NSTE-ACS.

IVB = intravenous bolus.

v. Platelet function testing
  (a) Although platelet function can be evaluated by platelet function testing or genotyping, neither is routinely done in the clinical setting.
  (b) Clinical outcomes with use of platelet function testing to modify antiplatelet therapy (i.e., high-dose vs. standard-dose clopidogrel) in patients undergoing PCI with high on-treatment platelet reactivity have been negative to date. Outcomes with prospective genotype-guided antiplatelet therapy (CYP2C19) from large cohorts of patients undergoing PCI are forthcoming.
  (c) Routine use of platelet function and genetic testing is not currently recommended (class IIb: for select patients).

f. Anticoagulant recommendations
   i. An anticoagulant should be administered to all patients with ACS in addition to antiplatelet therapy to reduce the risk of intracoronary and catheter thrombus formation (Tables 8 and 9), irrespective of initial treatment strategy.
   ii. Use of anticoagulants is typically concentrated in the procedural setting, though use may continue for a finite period after the procedure.
   iii. Selection and use among agents may depend on ACS presentation, timing or dose of preprocedural antiplatelet medication, clot burden during procedure, and estimated risk of bleeding during procedure.
   iv. Anticoagulants increase the risk of bleeding and will require some type of monitoring for agent-specific risks.

Table 8. Anticoagulant Management Strategies in ACS

Management Strategy	Class I Recommendations[a]
STEMI (PPCI)	UFH, bivalirudin
STEMI, with fibrinolytic[b] therapy	UFH, enoxaparin, fondaparinux
NSTE-ACS, early invasive strategy	Enoxaparin, bivalirudin,[c] UFH
NSTE-ACS, ischemia-guided strategy	Enoxaparin, fondaparinux,[d] UFH

[a]Class IIa = reasonable to be performed or administered; class IIb = may be considered; class III = not to be administered or harmful.

[b]Fibrinolytics preferred when PCI cannot be done within 120 min of first medical contact (class I). Door-to-needle time goal < 30 min. Those who receive fibrinolytic therapy should receive anticoagulation after fibrinolysis for at least 48 hr with IV UFH or IV/SC enoxaparin during hospitalization, up to 8 days (preferred, selected patients), or IV/SC fondaparinux during hospitalization, up to 8 days.

[c]If bleeding risk is high, it is reasonable to use bivalirudin monotherapy in preference to UFH plus GP IIb/IIIa inhibitor (class IIa).

[d]Fondaparinux should not be used as the sole anticoagulant to support PCI. Give additional anticoagulant during revascularization if fondaparinux was initially chosen as the anticoagulant strategy. Fondaparinux is given a class I recommendation in the 2014 NSTE-ACS guidelines (for an ischemia-guided strategy) and a class III or harmful recommendation in the 2011 PCI and 2013 STEMI guidelines when PCI is indicated.

PPCI = primary percutaneous coronary intervention; SC = subcutaneous(ly).

g. Anticoagulant agents
   i. UFH
      (a) Exerts its effects as an indirect thrombin inhibitor on fibrin-bound clots
      (b) Given as an intravenous bolus with or without infusion and adjusted according to activated partial thromboplastin time (aPTT) or activated clotting time (ACT) to maintain therapeutic anticoagulation according to specific hospital protocol, usually continued for 48 hours or until PCI
         (1) Intravenous UFH: Initial bolus of 60 units/kg (maximum 4000 units)
         (2) Initial infusion of 12 units/kg/hour (maximum 1000 units/hour)
      (c) Risks include bleeding, thrombocytopenia, and HIT with or without thrombosis.
      (d) Monitoring includes aPTT or ACT, Hgb/Hct, and Plt.
      (e) Unlike other anticoagulants, UFH is not renally cleared and can be used safely in those with renal impairment.
   ii. Enoxaparin: Molecular weight is one-third of UFH with balanced anti-factor Xa (anti-Xa) and anti-IIa activity.
      (a) Given as subcutaneous injection at least 2 inches on either side of the navel at a 90-degree angle into 1 inch of pinched skin (avoid injection into muscle); alternate dosing sites
         (1) Dosing varies depending on the reperfusion strategy and the time from the last dose to the procedure (Table 9).
         (2) 30-mg intravenous bolus given in STEMI (if age younger than 75) and in select patients with NSTE-ACS

(3) Specific periprocedural dosing for PCI in relation to time of last subcutaneous dose (see section (b) that follows for patients undergoing an invasive strategy)
(4) Decrease dosing interval to once daily when CrCl is less than 30 mL/minute.
(b) Does not require routine anti-Xa monitoring; requires SCr to calculate CrCl for dosing; monitor Hgb, Hct, Plt
(c) Risks include bleeding, injection site hematomas, spinal or epidural hematomas, retroperitoneal hematoma/bleeding, thrombocytopenia including HIT with or without thrombosis, mechanical prosthetic valve thrombosis (in pregnancy)

iii. Fondaparinux
(a) Selective inhibitor of activated factor X
(b) Longest half-life of anticoagulants (17 hours)
(c) Given as a subcutaneous injection into fatty tissue at a 90-degree angle into a pinched skinfold; alternate dosing sites between the left and right anterolateral and posterolateral abdominal wall
(1) Dosing NSTE-ACS: 2.5 mg subcutaneously daily, continued for the duration of hospitalization or until PCI
(2) Not to be used as the sole anticoagulant during PCI (class III)
(3) Contraindicated if CrCl is less than 30 mL/minute
(d) Does not require routine anti-Xa monitoring; requires SCr to calculate CrCl to assess for contraindication; monitor Hgb, Hct, Plt
(e) Risks include bleeding, thrombocytopenia, and spinal or epidural hematomas.
(f) No increased risk of HIT

iv. Bivalirudin
(a) A direct thrombin inhibitor; directly inhibits thrombin in both circulating and bound clots and inhibits thrombin-mediated platelet aggregation
(b) Given as an intravenous bolus with fixed-rate infusion and usually continued until the end of PCI (with or without delay after infusion in some high-risk patients)
(1) Early invasive strategy dosing: 0.1-mg/kg LD followed by 0.25 mg/kg per hour (only in patients with planned PCI), continued until diagnostic angiography or PCI
(2) PCI dosing: 0.75-mg/kg intravenous bolus, 1.75 mg/kg/hour intravenously continued throughout the procedure
(3) Adjust the infusion rate to 1 mg/kg/hour when the CrCl is less than 30 mL/minute or to 0.25 mg/kg/hour in patients receiving hemodialysis.
(4) Can extend duration of infusion for up to 4 hours after procedure for prolonged antiplatelet protection
(c) Does not require monitoring for adjustment during PCI; monitor SCr (adjustment required for infusion only in those with impaired CrCl), Hgb, Hct, Plt
(d) Can be given in patients with history of or suspected HIT undergoing PCI

h. Guideline recommendations for specific anticoagulants
i. In an **ischemia-guided strategy**, UFH, enoxaparin, and fondaparinux are class I recommended options.
ii. In an **invasive strategy**, UFH, enoxaparin, and bivalirudin are class I recommended options.
(a) Fondaparinux should not be used as the sole anticoagulant to support PCI (class III). An additional 85 units/kg of intravenous UFH is required immediately before PCI revascularization to reduce the risk of catheter thrombosis if fondaparinux was initially chosen as the anticoagulant strategy if no GP IIb/IIIa inhibitor is used and 60 units/kg intravenously if a GP IIb/IIIa inhibitor is used; re-bolus as needed according to target ACT.
(b) Use of enoxaparin during PCI may be reasonable in patients treated with upstream subcutaneous enoxaparin with an ischemia-guided strategy.

(1) An additional dose of 0.3 mg/kg of intravenous enoxaparin should be administered at the time of PCI to patients who have received fewer than two therapeutic subcutaneous doses or who received the last subcutaneous dose 8–12 hours before PCI.
(2) Patients who have received enoxaparin within 8 hours of the last subcutaneous dose generally have adequate anticoagulation to undergo PCI without supplemental bolus.
(3) Patients who undergo PCI more than 12 hours after the last subcutaneous dose are usually treated with full-dose de novo anticoagulation with an established regimen (e.g., full-dose UFH or bivalirudin).

(c) In those at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist (class IIa).
(1) For patients who have received UFH, wait 30 minutes and then give a 0.75-mg/kg intravenous LD, followed by a 1.75-mg/kg/hour intravenous infusion.
(2) For patients already receiving a bivalirudin infusion, give an additional 0.5-mg/kg LD, and increase the infusion to 1.75 mg/kg/hour during PCI.

(d) Anticoagulant therapy is generally discontinued after PCI unless there is a compelling reason to continue.

iii. In patients undergoing **primary PCI**, either UFH or bivalirudin is preferred.

Table 9. Antithrombotic Dosing in ACS with or without PCI

	UFH	Enoxaparin (Lovenox)	Fondaparinux (Arixtra)	Bivalirudin (Angiomax)
Classification	—	LMWH	Factor Xa inhibitor	Direct thrombin inhibitor
NSTE-ACS	60 units/kg IVB (max 4000 units), 12 units/kg/hr IV (max 1000 units/hr) for 48 hr or until PCI; goal aPTT/anti-Xa according to hospital-specific protocol	1 mg/kg SC every 12 hr for 24–48 hr or until PCI or throughout hospitalization (up to 8 days); 30 mg IVB	2.5 mg SC daily	0.1 mg/kg IVB; then 0.25 mg/kg/hr IV (only for planned invasive strategy)
PCI	Supplemental doses to target ACT[a]; if GP IIb/IIIa inhibitors, UFH 50–70 units/kg IVB; if no GP IIb IIIa inhibitors, UFH 70–100 units/kg IVB	If last dose < 8 hr, nothing additional needed; if last dose > 8 hr, 0.3 mg/kg IVB if last dose 8–12 hr before or < 2 therapeutic doses received before PCI	Fondaparinux should not be used as a sole anticoagulant for PCI	0.75 mg/kg IVB, 1.75mg/kg/hr IV d/c at end of PCI, or continue for up to 4 hr after procedure if needed; hold UFH 30 min before administration

Table 9. Antithrombotic Dosing in ACS with or without PCI *(Cont'd)*

	Unfractionated Heparin	Enoxaparin (Lovenox)	Fondaparinux (Arixtra)	Bivalirudin (Angiomax)
STEMI ± primary PCI	Supplemental doses to target ACT[a]; if GP IIb/IIIa inhibitor, UFH 50–70 units/kg IVB; if no GP IIb/IIIa inhibitor, UFH 70–100 units/kg IVB	30 mg IVB, followed immediately by 1 mg/kg SC every 12 hr; do not exceed 100 mg on first two doses; if > 75 yr, omit bolus; 0.75 mg/kg SC every 12 hr; do not exceed 75 mg on first two doses	2.5 mg IVB; then 2.5 mg SC daily	0.75 mg/kg IVB, 1.75 mg/kg/hr IV
Dose adjustments and contraindications	Avoid if history of HIT	If CrCl < 30 mL/min, 1 mg/kg SC daily; avoid if history of HIT	Contraindicated if CrCl < 30 mL/min	Adjust infusion dose in severe renal dysfunction If CrCl < 30 mL/min, reduce infusion to 1 mg/kg/hr; if on hemodialysis, reduce infusion to 0.25 mg/kg/hr

[a]Target ACT is 250–300 s for HemoTec and 300–350 s for Hemochron without GP IIb/IIIa inhibitors and 200–250 s in patients given concomitant GP IIb/IIIa inhibitors.

ACT = activated clotting time; HIT = heparin-induced thrombocytopenia; IVB = intravenous bolus; LMWH = low-molecular-weight heparin.

5. **Fibrinolytic therapy** is indicated for patients with a STEMI in whom PCI cannot be done (Table 10).
   a. In the absence of contraindications (Table 11), fibrinolytic therapy should be given to patients with a STEMI (class I when onset of ischemic symptoms is within the previous 12 hours) when it is expected that primary PCI cannot be done within 120 minutes of first medical contact, with an ideal door-to-needle time of less than 30 minutes.
   b. When a fibrinolytic agent is given as a reperfusion strategy, UFH, enoxaparin, and fondaparinux are recommended.
   c. Patients undergoing reperfusion with fibrinolytics should receive anticoagulant therapy after fibrinolysis for at least 48 hours with intravenous UFH or intravenous/subcutaneous enoxaparin during hospitalization, up to 8 days (preferred, selected patients), or intravenous/subcutaneous fondaparinux during hospitalization, up to 8 days.
      i. UFH administration of a 60-unit/kg bolus (maximum 4000 units) and 12 units/kg/hour (maximum 1000 units/hour), to obtain an aPTT of 1.5–2.0 times control (about 50–70 seconds) for at least 48 hours
      ii. Enoxaparin 30 mg intravenously (if 75 or older, omit bolus), followed in 15 minutes by a 1-mg/kg subcutaneous injection (if 75 or older, 0.75 mg/kg) every 12 hours for the duration of index hospitalization, for up to 8 days, or until revascularization. Maximum 100 mg for the first two doses. If 75 or older, maximum 75 mg for the first two doses. If CrCl is less than 30 mL/minute, extend dosing interval to daily administration.
      iii. Fondaparinux administered with an initial 2.5-mg intravenous dose, followed in 24 hours by 2.5-mg/day subcutaneous injections (contraindicated if CrCl is less than 30 mL/minute) for the duration of the index hospitalization, for up to 8 days, or until revascularization

Table 10. Fibrinolytic Therapy

	Dosing
Alteplase (t-PA, Activase)	≤ 67 kg: 15 mg IVP over 1–2 min, then 0.75 mg/kg IV over 30 min (max 50 mg), then 0.5 mg/kg (max 35 mg) over 60 min > 67 kg: 15 mg IVP over 1–2 min, then 50 mg over 30 min, then 35 mg over 1 hr (max total dose 100 mg)
Reteplase (r-PA, Retavase)	10 units IVP; repeat 10 units IV in 30 min
Tenecteplase (TNK-t-PA, TNKase)	< 60 kg: 30 mg IVP; 60–69 kg: 35 mg IVP; 70–79 kg: 40 mg IVP; 80–89 kg: 45 mg IVP; > 90 kg: 50 mg IVP (~0.5 mg/kg)

IVP = intravenous push; r-PA = recombinant plasminogen activator; t-PA = tissue plasminogen activator.

Table 11. Contraindications to Fibrinolytic Therapy

Relative Contraindications	**Absolute Contraindications**
BP > 180/110 mm Hg on presentation or history of chronic poorly controlled HTN History of ischemic stroke > 3 mo before Recent major surgery (< 3 wk before) Traumatic or prolonged CPR (> 10 min) Recent internal bleeding (within 2–4 wk) Active peptic ulcer Noncompressible vascular punctures Pregnancy Known intracranial pathology (dementia) OAC therapy	Any prior hemorrhagic stroke Ischemic stroke within 3 mo (except in past 4½ hr) Intracranial neoplasm or arteriovenous malformation Active internal bleeding Aortic dissection Considerable facial trauma or closed-head trauma in past 3 mo Intracranial or intraspinal surgery within 2 mo Severe uncontrolled HTN (unresponsive to emergency therapy) For streptokinase,[a] treatment within previous 6 mo (if considering streptokinase again)

[a]Streptokinase is no longer marketed in the United States but is available in other countries.

BP = blood pressure; CPR = cardiopulmonary resuscitation.

D. Long-term Management After ACS
   1. DAPT
      a. Given at least 12 months after ACS
      b. DAPT reduces mortality after ACS, regardless of whether the patient received stenting.
         i. Aspirin should be continued indefinitely at a maintenance dose of 81 mg daily in all patients after ACS (class I).
         ii. In patients who were treated with an ischemia-guided therapy, aspirin plus either clopidogrel 75 mg daily or ticagrelor 90 mg twice daily should be continued for up to 12 months.
         iii. After PCI (bare metal stent or drug-eluting stent), aspirin plus clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be continued for at least 12 months.
      c. Early discontinuation of DAPT
         i. Early discontinuation is reasonable when the risk of morbidity exceeds the expected benefit (class IIa).
            (a) DAPT should be continued after ACS (with or without stent) for at least 12 months (class I).
            (b) Shorter-duration DAPT can be considered for patients with stable ischemic heart disease who have undergone PCI with elective stent placement (class I, 6 months duration for elective PCI).

ii. In general, shorter durations of DAPT are appropriate for those with a lower ischemic risk and a high bleeding risk, whereas longer-duration DAPT may be reasonable for patients with a higher ischemic risk and a lower bleeding risk.
iii. Trials comparing shorter DAPT durations have evaluated newer-generation stents in all patients undergoing PCI (including elective cases).
iv. Compared with first-generation stents, newer-generation stents have an improved safety profile and a lower risk of stent thrombosis.
v. Proton pump inhibitors can reduce the risk of gastrointestinal (GI) bleeding from DAPT.

d. Long-term DAPT
i. In general, longer-duration DAPT may be reasonable for patients at a higher ischemic risk with a lower bleeding risk.
ii. Trials evaluating the need for an extended DAPT duration (greater than 12 months) in patients with and without ACS undergoing PCI show a reduction in stent thrombosis and ischemia end points with increased bleeding for patients continued on DAPT beyond 12 months.
iii. The risk of stent thrombosis is greater on DAPT cessation; however, continued DAPT beyond 1 year is not associated with reduced CV or total mortality.
iv. A longer duration of $P2Y_{12}$ inhibitor therapy is an individualized approach according to the patient's risk of ischemia and bleeding.
(a) DAPT may be reasonable beyond 12 months if the patient is at high risk and has no significant history of bleeding while receiving DAPT (class IIb).
(b) A DAPT score derived from the DAPT study may help in deciding whether to prolong or extend DAPT in patients treated with coronary stent implantation (Table 12).
(1) Derived from the DAPT study, which included 11,648 patients with mainly clopidogrel as the $P2Y_{12}$ inhibitor
(2) For those with a high DAPT score (2 or greater), prolonged DAPT reduces net (ischemic plus bleeding) events.
(3) For those with a low DAPT score (less than 2), the benefit-risk ratio for prolonged DAPT is not favorable (increased bleeding without a reduction in ischemic events).
(4) Duration of DAPT for more or less than 12 months should jointly be made by the clinician and the patient, balancing the risks of stent thrombosis and ischemic complications with the risks of bleeding.
v. Ticagrelor has been shown to reduce CV end points of death, MI, and revascularization to a greater extent than placebo at a reduced dose of 60 mg twice daily (after at least 12 months of 90 mg twice daily) with less bleeding than extended use of 90 mg twice daily (N Engl J Med 2015;372:1791-800).

2. β-Blockers
a. Indicated for all patients unless contraindicated
b. If not initiated orally within the first 24 hours, reevaluate for possible initiation before discharge.
c. Continue for at least 3 years (when EF is greater than 40%).
d. If moderate or severe LV failure, initiate carvedilol, bisoprolol, or metoprolol succinate with gradual titration. Continue indefinitely in patients with an EF less than 40%.

3. Angiotensin-converting enzyme (ACE) inhibitors
a. ACE inhibitors should be initiated and continued indefinitely for all patients with an LVEF of 40% or less and in those with hypertension, diabetes mellitus, or stable chronic kidney disease, unless contraindicated.
b. ACE inhibitors may be acceptable in all other patients with cardiac or other vascular disease.
c. Angiotensin receptor blockers (ARBs) are indicated if the patient has contraindications to or is intolerant of ACE inhibitors.
d. Contraindications include hypotension, pregnancy, and bilateral renal artery stenosis.

Table 12. DAPT Score to Determine Favorability of Prolonged DAPT

Factors Used to Calculate DAPT Score	Add Points for Total Score[a]
Age ≥ 75	-2
Age 65–74	-1
Current tobacco user	1
Diabetes mellitus	
NSTEMI or STEMI at presentation	
Prior MI or PCI	
Stent diameter < 3 mm	
Paclitaxel-eluting stent	
CHF or LVEF < 30%	2
Saphenous vein graft PCI	2

[a]A score ≥ 2 favors prolonged DAPT; a score < 2 is of unfavorable risk-benefit.

CHF = congestive heart failure; DAPT = dual antiplatelet therapy; LVEF = left ventricular ejection fraction.

Information from: Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082-115; and Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 2016;315:1735-49.

4. Aldosterone receptor blockers
    a. Indicated in patients who are already receiving an ACE inhibitor and β-blocker after MI and who have an LVEF of 40% or less and either symptomatic HF or diabetes, unless contraindicated
    b. Contraindications include hyperkalemia (potassium [K^+] 5.0 or greater), CrCl less than 30 mL/minute, and SCr greater than 2.5 mg/dL in men and greater than 2.0 mg/dL in women.
5. Lipid-lowering therapies
    a. High-intensity statins are indicated in all patients after ACS without contraindication and are generally initiated as soon as possible within the first 24 hours.
    b. In high-risk patients achieving a less-than-expected response to statins (less than a 50% reduction in low-density lipoprotein cholesterol [LDL]), or in those who are completely statin intolerant, non-statin therapy may be considered for CV benefit.
    c. Depending on the additional desired LDL percentage reduction, either ezetimibe or a PCSK9 inhibitor can be considered in combination with statin therapy in very high-risk patients.
    d. Both ezetimibe and PCSK9 inhibitors (given in combination with statins) reduce CV end points.
    e. An LDL goal of less than 70 mg/dL is reasonable in patients post-ACS.
6. Pain control
    a. NSAIDs and select cyclooxygenase-2 inhibitors (class III) should be discontinued at the time of presentation because they have been associated with an increased risk of major adverse cardiac events.
    b. Before discharge, the patient's musculoskeletal discomfort should be addressed, and a stepped-care approach should be used to select therapy.
    c. Pain should be treated with acetaminophen, nonacetylated salicylates, tramadol, or narcotics at the lowest dose to control symptoms.
    d. It is reasonable to use nonselective NSAIDs, such as naproxen, if initial therapy is insufficient.
        i. Monitor regularly for sustained hypertension, edema, worsening renal function, or GI bleeding.
        ii. If these occur, consider dose reduction or discontinuation.

7. Vaccination
    a. Pneumococcal vaccination is recommended for patients 65 and older and in high-risk patients (including smokers with asthma) with CV disease.
    b. An annual influenza vaccination is recommended for patients with CV disease.
8. Patient education
    a. All patients should be counseled on the duration of DAPT and the avoidance of premature discontinuation.
    b. Patients should be educated about appropriate cholesterol management, blood pressure control, smoking cessation, and lifestyle management.
    c. Risk factor modification should be addressed in all patients after ACS.
9. Cardiac rehabilitation: All eligible patients should be referred to a comprehensive CV rehabilitation program.

E. Special Populations
1. Antiplatelet recommendations in patients going on to CABG
    a. Aspirin should be continued preoperatively to patients undergoing CABG (81–325 mg).
    b. In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery and prasugrel for at least 7 days before surgery.
    c. In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding.
    d. In patients referred for CABG, short-acting GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 hours before surgery to limit blood loss and transfusion.
2. Combined oral anticoagulant therapy and antiplatelet therapy in patients with atrial fibrillation (AF) undergoing PCI
    a. Triple therapy with an oral anticoagulant, low-dose aspirin, and a $P2Y_{12}$ inhibitor should be minimized because it substantially increases the risk of bleeding.
    b. New AF guidelines and consensus recommendations based on clinical trial data represent a paradigm shift from older management with triple therapy:
        i. Many trials have shown that double antithrombotic therapy (anticoagulant plus $P2Y_{12}$ inhibitor without aspirin) reduces bleeding events compared with triple therapy without signal for increasing ischemic events.
            (a) Double therapy with a P2Y12 inhibitor plus dose-adjusted vitamin K antagonist (WOEST trial)
            (b) Double therapy with a P2Y12 inhibitor plus rivaroxaban 15 mg daily (PIONEER AF)
            (c) Double therapy with a P2Y12 inhibitor plus dabigatran 150 mg twice daily (RE-DUAL)
            (d) Double therapy with a P2Y12 inhibitor plus apixaban 5 mg twice daily (AUGUSTUS)
        ii. De-escalation time from triple to dual therapy varies depending on ischemic and bleeding risks.
            (a) Aspirin therapy can be discontinued at time of discharge or can be continued for 1–3 months, depending on risks.
            (b) Triple therapy may be extended beyond hospital discharge for a limited time (i.e., 1–3 months) in select patients at the highest risk of ischemic events and lowest risk of bleeding.
        iii. In AF, direct-acting oral anticoagulants are preferred to vitamin K antagonists because of their reduced bleeding risk.
            (a) Warfarin remains the drug of choice in patients with mechanical heart valves and in those with moderate to severe mitral stenosis.
            (b) If warfarin is used for triple therapy, it is reasonable to maintain the international normalized ratio (INR) at the lower end of the therapeutic range (i.e., 2–2.5).

iv. Clopidogrel is the preferred $P2Y_{12}$ inhibitor, though ticagrelor may be reasonable in patients at high ischemic/thrombotic and low bleeding risks (i.e., avoid prasugrel).
(a) Discontinue antiplatelet therapy at 1 year in most patients.
(b) However, the same considerations apply for shortening the duration (i.e., 6 months in those with high bleeding risk) and extending the duration (i.e., more than 12 months in those at high thrombotic risk with low bleeding risk) as for those without AF.

c. Proton pump inhibitors should be considered for those with a history of GI bleeding (and is reasonable in those without a known history of GI bleeding) who need triple antithrombotic therapy.

3. Older patients (i.e., 75 or older)
a. Doses should be individualized by weight or CrCl to reduce adverse events caused by age-related changes in pharmacokinetics and dynamics, volume of distribution, comorbidities, drug interactions, and increased drug sensitivity.
b. Bivalirudin, rather than GP IIb/IIIa inhibitors plus UFH, is reasonable in older patients, given its similar efficacy but less risk of bleeding (class IIa).
c. If enoxaparin is used as an anticoagulant in older patients (older than 75), the bolus should be omitted, and the dosing strategy should be 0.75 mg/kg subcutaneously every 12 hours; should not exceed 75 mg for the first two doses
d. CABG may be preferred to PCI in older patients, particularly those with diabetes mellitus or complex three-vessel disease (e.g., SYNTAX score greater than 22), with or without involvement of the proximal left anterior descending artery.

4. Chronic kidney disease
a. CrCl should be estimated in patients with ACS, and doses of renally cleared medications should be adjusted accordingly.
b. Patients with chronic kidney disease undergoing coronary and LV angiography should receive adequate hydration and reduced contrast volume.

5. Women
a. Women of all ages have higher rates of in-hospital and long-term complications from ACS than men.
b. Women derive the same benefit from aspirin, $P2Y_{12}$ inhibitors, anticoagulants, β-blockers, ACE inhibitors, and statins as men, but women may be at higher risk of adverse events.
i. Women have a higher rate of bleeding complications, renal failure, and vascular complications.
ii. A risk score has been developed to reduce bleeding risk.
c. Women with NSTE-ACS and high-risk features (e.g., troponin positive) should undergo an early invasive strategy.
d. Women with NSTE-ACS and low-risk features should not undergo early invasive treatment because of the lack of benefit and the potential for harm (class III).
e. Hormone therapy with estrogen plus progestin, or estrogen alone, should not be initiated for secondary prevention and should not be continued in previous users unless the benefits outweigh the estimated risks.
i. Hormone therapy increases the risk of thrombotic events, especially in the first year of therapy, and does not provide CV protection.
ii. Women who are more than 1 year past the initiation of hormone therapy who want to continue such therapy for another compelling indication should weigh the risk-benefit, recognizing the greater risk of CV events and breast cancer (combination therapy) or stroke (estrogen).

Patient Cases

1. A 66-year-old woman (weight 70 kg) with a history of MI, hypertension, hyperlipidemia, and diabetes mellitus presents with sudden-onset diaphoresis, nausea, vomiting, and dyspnea, followed by a bandlike upper chest pain (8/10) radiating to her left arm. She had felt well until 1 month ago, when she noticed her typical angina was occurring with less exertion. Her ECG reveals ST-segment depression in leads II, III, and aVF and hyperdynamic T waves and positive cardiac enzymes. Blood pressure is 150/90 mm Hg, and all laboratory results are normal; SCr is 1.2 mg/dL. Home medications are aspirin 81 mg/day, simvastatin 40 mg every night, metoprolol 50 mg twice daily, and metformin 1 g twice daily. Which regimen is best for this patient?
   A. Aspirin 325 mg, ticagrelor 180 mg one dose, and UFH 60-unit/kg bolus; then 12 units/kg/hour titrated to 50–70 seconds with an early invasive approach.
   B. Aspirin 325 mg and enoxaparin 70 mg subcutaneously twice daily with an early invasive approach.
   C. An ischemia-guided strategy with tirofiban 25 mcg/kg; then 0.15 mg/kg/minute plus enoxaparin 80 mg subcutaneously twice daily, aspirin 325 mg/day, and clopidogrel 300 mg one dose; then 75 mg once daily.
   D. An ischemia-guided strategy with aspirin 325 mg and ticagrelor 180 mg one dose; plus UFH 70-unit/kg bolus; then 15 units/kg/hour.

2. A 45-year-old patient underwent an elective percutaneous transluminal coronary angioplasty and drug-eluting stent placement in her right coronary artery. Which best represents the minimum time DAPT should be continued?
   A. 1 month.
   B. 3 months.
   C. 6 months.
   D. 12 months.

3. A 52-year-old man (weight 100 kg) with a history of hypertension and hypertriglyceridemia presents at a major university teaching hospital with a cardiac catheterization laboratory. He has had 3 hours of crushing 10/10 substernal chest pain radiating to both arms that began while he was eating his lunch (seated), which is accompanied by nausea, diaphoresis, and shortness of breath. He has never before had chest pain of this character or intensity. He usually can walk several miles without difficulty and smokes 1.5 packs/day of cigarettes. Home medications are lisinopril 2.5 mg/day and aspirin 81 mg daily. Current vital signs include heart rate 68 beats/minute and blood pressure 178/94 mm Hg. His ECG reveals a 3-mm ST-segment elevation in leads V_2–V_4, I, and aVL. Serum chemistry values are within normal limits. The first set of cardiac markers shows positive troponins, 0.8 mcg/L (normal defined as less than 0.1 mcg/L). Which regimen is best for this patient's STEMI?
   A. Reperfusion with primary PCI and stenting of occluded artery, together with tirofaban 25 mcg/kg; then 0.15 mg/kg/minute, clopidogrel 300 mg one dose, and aspirin 325 mg one dose.
   B. Reperfusion with a reteplase 10-unit bolus twice, 30 minutes apart, plus a UFH 60-unit/kg bolus and a 12-unit/kg/hour infusion, clopidogrel, and aspirin.
   C. Reperfusion with tenecteplase 25-mg intravenous push one dose, enoxaparin 30-mg intravenous bolus plus 100 mg subcutaneously twice daily, aspirin 325 mg one dose, ticagrelor 180 mg one dose, and bivalirudin 0.75 mg/kg followed by 1.75 mg/kg/hour.
   D. Reperfusion with primary PCI with stenting, prasugrel 60 mg one dose, aspirin 325 mg one dose, and bivalirudin 0.75 mg/kg followed by 1.75 mg/kg/hour.

Patient Cases *(Cont'd)*

4. A 76-year-old male smoker (weight 61 kg) has a history of hypertension, benign prostatic hypertrophy, and lower back pain. Three weeks ago, he began to have substernal chest pain with exertion (together with dyspnea), which radiated to both arms and was associated with nausea and diaphoresis. These episodes have increased in frequency to four or five times daily; they are relieved with rest. He has never had an ECG. Today, he awoke with 7/10 chest pain and went to the ED of a rural community hospital 2 hours later. He was acutely dyspneic and had ongoing pain. Home medications are aspirin 81 mg/day for 2 months, doxazosin 2 mg/day, and ibuprofen 800 mg three times daily. Vital signs include heart rate 42 beats/minute (sinus bradycardia) and blood pressure 104/48 mm Hg. Laboratory results include blood urea nitrogen (BUN) 45 mg/dL, SCr 2.5 mg/dL, and troponin 1.5 ng/L (normal value less than 0.1 ng/L). His ECG reveals a 3-mm ST-segment elevation. Aspirin, ticagrelor, and sublingual nitroglycerin were given in the ED. The nearest hospital with a catheterization laboratory facility is 2½ hours away. Which regimen is best?

   A. Give alteplase 15 units intravenously plus enoxaparin 30-mg intravenous bolus.

   B. Use an ischemia-guided treatment strategy with UFH 4000-unit intravenous bolus, followed by 800 units intravenously per hour.

   C. Give tenecteplase 35 mg intravenously plus UFH 4000-unit intravenous bolus followed by 800 units intravenously per hour.

   D. Transfer the patient to a facility for primary PCI.

II. ACUTE DECOMPENSATED HEART FAILURE

A. Precipitating Factors
   1. Medication related (nonadherence to medications, recent addition of negative inotropic drugs, initiation of medications that enhance salt retention, excessive alcohol or illicit drug use)
   2. Disease related (nonadherence to sodium or fluid restriction, acute myocardial ischemia, uncorrected high blood pressure, pulmonary embolus, AF or other arrhythmias, concurrent infections, other acute CV disorders)

B. Diagnosis
   1. Must include a detailed history and physical examination
   2. B-type natriuretic peptide (BNP) or NT-proBNP is useful to support the diagnosis and establish the prognosis for acute decompensated heart failure (ADHF).
      a. Useful for excluding ADHF in patients with dyspnea of unknown etiology (ADHF can be excluded when results are less than 100 pg/mL and less than 300 pg/mL, for BNP and NT-proBNP, respectively)
      b. NT-proBNP cutpoints of 450, 900, and 1800 pg/mL (for ages younger than 50, 50–75, and older than 75, respectively)
      c. May be elevated with older age, female sex, renal dysfunction, and other cardiopulmonary disorders like pulmonary embolism
      d. NT-proBNP is preferred in patients receiving angiotensin receptor neprilysin inhibitor (ARNI) therapy because BNP concentrations may be affected by ARNI therapy
   3. Hemodynamic monitoring (Table 13)
      a. Routine use of hemodynamic monitoring with invasive intravenous lines (e.g., Swan-Ganz pulmonary artery catheters) is not recommended; however, signs and symptoms of congestion and perfusion (Table 14) or noninvasive means to determine hemodynamic values are commonly used to determine status of decompensation.

b. Hemodynamic monitoring with pulmonary artery catheters helps in evaluating patients refractory to initial therapy, patients with unknown or unclear volume status, and patients with clinically significant hypotension or worsening renal function.
c. Use of hemodynamic monitoring for mechanical circulatory support is beyond the scope of this chapter.

Table 13. Hemodynamic Values in Patients with ADHF and Sepsis

Parameter	Normal Value	Typical ADHF Value	Typical Sepsis Value
Mean arterial pressure[a] (MAP; mm Hg)	80–100	60–80	60–80
Heart rate (HR; beats/min)	60–80	70–90	90–100
Cardiac output (CO; L/min)[b]	4–7	2–4	5–8
Cardiac index (CI; L/min/m^2)[c]	2.8–3.6	1.3–2	3.5–4
Pulmonary capillary wedge pressure (mm Hg)[d]	8–12[b]	18–30	5–8
Systemic vascular resistance (SVR; dynes/s/cm^5)[e]	900–1400	1500–3000	300–800
Central venous pressure (CVP; mm Hg)[f]	2–6	6–15	2–6

[a]MAP = diastolic blood pressure (DBP) + [⅓(SBP − DBP)].
[b]CO = stroke volume × HR.
[c]CI = CO/body surface area.
[d]15–18 mm Hg is often desired or optimal in patients with HF to ensure optimal filling pressures.
[e]SVR = [(MAP − CVP)/CO] × 80.
[f]BP = CO × SVR.
ADHF = acute decompensated heart failure; SVR = systemic vascular resistance.

C. Clinical Presentation
1. Patients with ADHF can be categorized into four subsets on the basis of fluid status and cardiac function (Figure 2).
2. "Wet or dry" is commonly used to describe volume status.
3. "Warm or cold" is used to describe cardiac function or ability to perfuse tissues.

Table 14. Signs and Symptoms of ADHF

Congestion (elevated PCWP)	Hypoperfusion (low CO)
Dyspnea on exertion or at rest	Fatigue
Orthopnea, paroxysmal nocturnal dyspnea	Altered mental status or sleepiness
Peripheral edema	Cold extremities
Rales	Worsening renal function
Early satiety, nausea, or vomiting	Narrow pulse pressure
Ascites	Hypotension
Hepatomegaly, splenomegaly	Hyponatremia
Jugular venous distension	
Hepatojugular reflux	

CO = cardiac output; PCWP = pulmonary capillary wedge pressure.

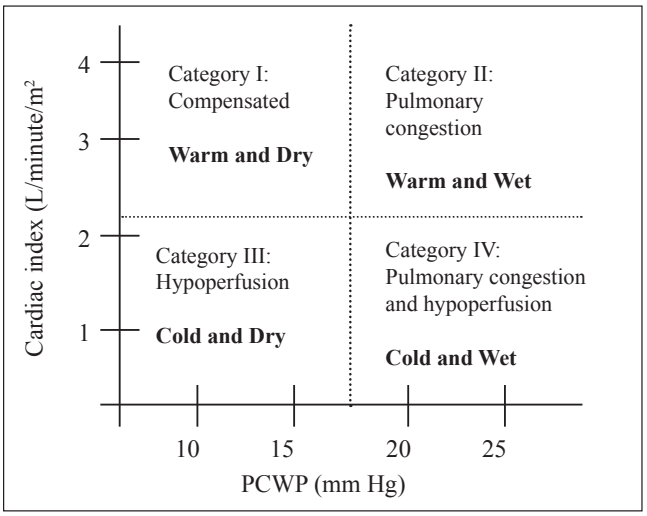

Figure 2. Forrester hemodynamic subsets based on signs and symptoms or hemodynamic parameters in acute decompensated heart failure.

PCWP = pulmonary capillary wedge pressure.

D. ADHF Therapy Overview (Box 1; Table 15)
   1. Address any precipitating factors, when possible.

Box 1. Overview of ADHF Guideline Recommendations

Diuretic therapy Recommended as IV loop diuretics for patients with fluid overload. Change to PO route on day before discharge, if possible When response to diuretics is minimal, the following options should be considered: • Fluid and sodium restriction • Initiation of increased doses or continuous infusion of loop diuretic • Addition of a second diuretic with a different mechanism of action (metolazone, hydrochlorothiazide, chlorothiazide) • Ultrafiltration
Inotropic therapy May be considered to relieve symptoms and improve end-organ function in patients with reduced LVEF and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if • Marginal SBP (< 90 mm Hg) • Symptomatic hypotension despite adequate filling pressure • No response to or intolerance of IV vasodilators May be considered in similar patients with evidence of fluid overload if they respond poorly to IV diuretics or manifest diminished or worsening renal function
Vasodilator therapy May be considered in addition to IV loop diuretics to rapidly improve symptoms in patients with acute pulmonary edema or severe hypertension (if symptomatic hypotension absent) May be considered in patients with persistent symptoms despite aggressive diuretics and PO drug therapy When adjunctive therapy is necessary in addition to loop diuretics, IV vasodilators should be considered over inotropic drugs

ADHF = acute decompensated heart failure; IV = intravenous(ly); LVEF = left ventricular ejection fraction.

2. Relieve signs and symptoms of congestion and tissue hypoperfusion.
   a. The main drug classes used to treat ADHF include diuretics, inotropes, and vasodilators.
   b. No therapy studied to date has been shown conclusively to decrease mortality.
   c. Treatments are directed toward relieving symptoms, restoring perfusion, and minimizing further cardiac damage and adverse events and are guided by cardiac output (CO) and volume status.
3. Reduce in-hospital mortality and minimize risk of rehospitalization.
4. Optimize GDMT.

Table 15. General ADHF Management Based on Hemodynamic Subset[a]

Subset and Description	Treatment
Subset I: Warm and Dry (normal parameters) (PCWP 15–18 mm Hg[b] and CI > 2.2 L/min/m^2)	Optimize guideline-directed medical therapies (PO medications)
Subset II: Warm and Wet (pulmonary or peripheral congestion) (PCWP > 18 mm Hg and CI > 2.2 L/min/m^2)	IV diuretics at a dose that equals or exceeds pre-admission dose (up to 2.5-fold) ± IV vasodilators (venous[c]) for rapid relief of pulmonary congestion or (arterial) in the absence of hypotension If symptoms persist, adjunctive strategies[d] to overcome diuretic resistance may be necessary
Subset III: Cold and Dry (hypoperfusion ± orthostasis) (PCWP 15–18 mm Hg[b] and CI < 2.2 L/min/m^2)	If PCWP < 15 mm Hg, IVF until PCWP = 15–18 mm Hg If PCWP ≥ 15 mm Hg, SBP < 90 mm Hg, IV inotrope[e] If PCWP ≥ 15 mm Hg, SBP ≥ 90 mm Hg, IV vasodilator (arterial[f]) ± IV vasopressor,[g] if needed
Subset IV: Cold and Wet (pulmonary/peripheral congestion + hypoperfusion) (PCWP > 18 mm Hg and CI < 2.2 L/min/m^2)	IV diuretics + If SBP ≥ 90 mm Hg, IV vasodilator (arterial[f]) If SBP < 90 mm Hg, IV inotrope[e] ± IV vasopressor,[g] if needed

[a]Patients may be categorized into a hemodynamic subset on the basis of signs and symptoms or invasive hemodynamic monitoring.

[b]Goal PCWP is 8–12 mm Hg in a normal patient and 15–18 mm Hg in a patient with HF. If PCWP < 15 mm Hg in a patient with HF, either remove fluid restriction or cautiously administer fluids until PCWP is 15–18 mm Hg and then reassess CI.

[c]Venous vasodilator: Reduces PCWP.

[d]Adjunctive strategies for overcoming diuretic resistance include increasing the loop diuretic dose; changing to a continuous infusion; adding a diuretic with an alternative mechanism of action, an IV vasodilator, or an IV inotrope; and, in select patients, using ultrafiltration or a vasopressin antagonist.

[e]Compelling reason for inotrope = SBP < 90 mm Hg, symptomatic hypotension, or worsening renal function.

[f]Arterial vasodilator: Reduce systemic vascular resistance with compensatory increase in CI.

[g]IV vasopressors may be required when marked hypotension precludes the use of traditional IV inotropes (e.g., septic or cardiogenic shock) but are generally avoided in ADHF.

CI = cardiac index; IV = intravenous(ly); IVF = intravenous fluid; PCWP = pulmonary capillary wedge pressure; PO = oral(ly).

E. Chronic HF Therapy in the Setting of Acute Decompensation
   1. It is recommended to continue guideline-directed medical therapies (GDMTs) during decompensation unless hemodynamic instability or contraindications exist (e.g., hypotension, cardiogenic shock) because discontinuing GDMT worsens outcomes.
   2. ACE inhibitors/ARBs, ARNIs
      a. Caution with initiation or titration during aggressive diuresis
      b. Increases in SCr (decrease in glomerular filtration rate of 20% or more) from ACE inhibitor use are not associated with worse outcomes.
      c. Consider discontinuation if worsening renal function after recent drug initiation or increased symptomatic hypotension, severe hyperkalemia (K greater than 5.5 mEq/L)

3. β-Blockers
    a. Do not discontinue in patients whose condition is stable on dose before admission (i.e., recent initiation or titration was not responsible for decompensation).
    b. Consider discontinuation if ADHF caused by recent drug initiation or increase, evidence of new or worsening low output or cardiogenic shock, symptomatic hypotension or bradycardia
    c. Initiation is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators, and inotropic agents.
    d. Should be initiated at a low dose only in stable, euvolemic patients
    e. Caution should be used when initiating in patients who have received inotropes during their hospital course.
4. Digoxin
    a. Continue at dose to achieve serum digoxin concentration of 0.5–0.8 ng/mL.
    b. Consider discontinuation in symptomatic bradycardia, life-threatening arrhythmias, elevated concentrations, or signs/symptoms of digoxin toxicity.
    c. Avoid discontinuation unless there is a compelling reason to do so, because digoxin withdrawal has been associated with worsening HF symptoms.
    d. Caution if renal function begins to deteriorate or often fluctuates

F. Diuretics (Box 2; Table 16): Used primarily to treat patients with pulmonary and peripheral congestion or wet (subset II or IV) HF
    1. Considered first-line therapy for management of ADHF associated with fluid overload
    2. No difference between bolus and continuous administration of intravenous diuretics
    3. Administering high-dose intravenous diuretic (2.5 times the previous oral dose) is associated with greater fluid removal.

Box 2. Diuretic Therapy for ADHF

Loop diuretics (ascending limb of loop of Henle)
Most widely used and most potent, effective at low CrCl (< 30 mL/min)
Furosemide most commonly used; furosemide 40 mg PO = furosemide 20 mg IV = bumetanide 1 mg IV or PO = torsemide 20 mg IV or PO
Thiazides (distal tubule)
Weak diuretics when used alone, less effective at low glomerular filtration rate (CrCl < 30 mL/min)
Reserved for add-on therapy when refractory to loop diuretics
Diuretic resistance
Increase dose before increasing frequency of loop diuretic (note ceiling effect at ~160–200 mg of IV furosemide)
Add a second diuretic with a different mechanism of action • Hydrochlorothiazide 25–50 mg PO daily,[a] metolazone 2.5–5 mg PO daily (30 min before loop diuretic administration) • Chlorothiazide 250–500 mg IV daily; consider if GI edema; generic is very expensive; reserve for NPO or refractory to other alternatives
Continuous infusion of loop diuretic: Furosemide 0.1 mg/kg/hr IV doubled every 4–8 hr, max 0.4 mg/kg/hr
Adverse effects: Electrolyte depletion (sodium, K^+, magnesium), worsening renal function

[a]Ceiling dose may vary depending on the CrCl.

GI = gastrointestinal; NPO = nothing by mouth.

Table 16. Loop Diuretic Pharmacokinetic and Pharmacodynamic Comparisons

Drug	Furosemide	Bumetanide	Torsemide	Ethacrynic Acid
PO equivalent dose	40 mg	1 mg	20 mg	50 mg
Bioavailability, %	10%–100% (avg 50%)	80%–100%	70%–100%	100%
PO to IV conversion	2:1	1:1	1:1	1:1
Usual maintenance dose	40–160 mg	1–5 mg	10–20 mg	25–50 mg
Ceiling dose (normal CrCl)	~160 mg	1–2 mg	10–20 mg	~200 mg
Onset (peak), PO	30–60 min (1 hr)	30–60 min (1–2 hr)	60 min	30 min
Onset of action (IV)	5 min	2–3 min	10 min	5 min
Metabolism	50% renal conjugation	50% hepatic	80% hepatic	66% renal
Half-life normal (HF)	1.5–2 hr (2.7 hr)	1 hr (1.3 hr)	3–4 hr (6 hr)	1–4 hr
Avg duration of effect	6–8 hr	4–6 hr	12–16 hr	6 hr

avg = average.

G. Vasodilator Therapy (Table 17)
   1. Used (with diuretics) primarily to manage pulmonary congestion or wet (subset II or IV) HF
      a. Use is limited to relief of dyspnea in those with intact blood pressure.
      b. No data to suggest intravenous vasodilators improve outcomes
   2. When adequate blood pressure is maintained, use in preference to inotropic therapy.
   3. Venodilators increase venous capacitance, resulting in lower preload to reduce myocardial stress.
      a. Limits ischemia and helps preserve cardiac tissue (i.e., nitroglycerin would be the drug of choice for patients with ADHF and active ischemia)
      b. Produces rapid symptomatic benefit by reducing pulmonary congestion (i.e., acute relief of shortness of breath while awaiting the onset of diuretic effects)
      c. Nitroglycerin is commonly used as a venodilator.
   4. Vasodilators with arterial vasodilating properties (nitroprusside) can also be used as an alternative to inotropes in patients with elevated systemic vascular resistance (SVR) and low CO.
      a. Sodium nitroprusside is usually reserved for patients:
         i. With invasive hemodynamic monitoring (i.e., pulmonary artery catheter)
         ii. Without end-organ dysfunction (i.e., to avoid cyanide and thiocyanate accumulation)
         iii. Only until hemodynamic stabilization is achieved
         iv. To ensure the reversibility of pulmonary hypertension during evaluation for mechanical circulatory support or transplantation
      b. Nesiritide was discontinued by the manufacturer in February 2018.
   5. Vasodilators should be avoided in patients with symptomatic hypotension (i.e., SBP less than 90 mm Hg).
   6. Frequent blood pressure monitoring is necessary.

Table 17. Vasodilator Therapy for ADHF

	Sodium Nitroprusside (Nipride)	IV Nitroglycerin
Mechanism of action	Nitric oxide–induced stimulation of GC to convert GTP to cGMP	Combines with sulfhydryl groups in vascular endothelium to create *S*-nitrosothiol compounds that mimic nitric oxide's stimulation of GC and production of cGMP
Clinical effects	Balanced arterial and venous vasodilator	Preferential venous vasodilator > arterial vasodilator, arterial vasodilation at high doses
Indication	Warm and wet ADHF, alternative to inotropes in cold and wet ADHF, hypertensive crises	Warm and wet ADHF, ACS, or hypertensive crises
Dosing	0.1–0.2 mcg/kg/min IV, increase by 0.2–3 mcg/kg/min every 10–20 min	5 mcg/min IV, increase by 5 mcg/min every 5–10 min up to 200 mcg/min
Typical dose	0.5–1 mcg/kg/min IV	25–100 mcg/min IV, titrated to response
Half-life	< 10 min	1–3 min
Elimination	Cyanide hepatically metabolized, thiocyanate renally excreted	Inactive metabolites in urine
AEs	Hypotension or cyanide or thiocyanate toxicity	Hypotension, reflex tachycardia, headache, tachyphylaxis

AE = adverse effect; cGMP = cyclic guanine monophosphate; CI = cardiac index; ET-1 = endothelin; GC = guanylate cyclase; GTP = guanosine triphosphate; HR = heart rate; NE = norepinephrine.

H. Inotropic Therapy (Table 18)
   1. Used primarily to manage hypoperfusion or cold (subset III or IV) HF
      a. Useful for symptom relief in patients with a low SBP (less than 90 mm Hg) or symptomatic hypotension
      b. Useful in patients with end-organ dysfunction (i.e., acute kidney injury, altered mental status, systemic hypoperfusion, hypotension, or CV collapse)
      c. Useful in patients whose disease is refractory to other HF therapies
      d. Useful as a bridge to an LV assist device or to a heart transplant or as palliative care
   2. It is important to confirm that patients in subset III have adequate filling pressures (i.e., pulmonary capillary wedge pressure [PCWP] 15–18 mm Hg) before administering inotropic therapy.
   3. Given the risk of sequelae, it is reasonable to consider vasodilators before inotropes.
      a. Both milrinone and dobutamine are proarrhythmic.
      b. Inotropes increase mortality compared with vasodilator therapy.
   4. Monitor continuously for arrhythmias.
   5. Differences in the pharmacologic effects of dobutamine and milrinone may confer advantages and disadvantages, but the choice of inotropic therapy is very individualized.
      a. Milrinone may be favored:
         i. To avoid tapering or discontinuing home β-blocker
         ii. When pulmonary artery pressures are high
      b. Dobutamine may be favored in:
         i. Severe hypotension
         ii. Bradycardia
         iii. Thrombocytopenia
         iv. Severe renal impairment

Table 18. Inotropic Therapy for ADHF

	Dobutamine (Dobutrex)	Milrinone (Primacor)
Mechanism of action	β1-Agonist: Stimulates AC to convert ATP to cAMP to ↑ CO; slight peripheral vasodilation	PDE inhibitor: Inhibits cAMP breakdown in heart to ↑ CO and in vascular smooth muscle to ↓ SVR
Clinical effects	Positive inotropic, chronotropic, lusitropic effects	Positive inotropic and lusitropic effects, no direct chronotropic effects
Indication	ADHF: Cold and wet (Forester subset IV) or cold and dry exacerbations (Forester III) (if PCWP > 15 mm Hg)	
Dosing	Start 2.5–5 mcg/kg/min IV; may titrate to max of 20 mcg/kg/min	50 mcg/kg IVB (rarely administered), then 0.1–0.2 mcg/kg/min IV; may titrate to max of 0.75 mcg/kg/min
Typical dose	5 mcg/kg/min IV	No bolus, 0.1–0.375 mcg/kg/min IV
Half-life	2 min	1 hr, prolonged to 2–3 hr if HF or CrCl < 50 mL/min
Elimination	Hepatically metabolized (inactive), renally eliminated	90% renal
AEs	Proarrhythmia, tachycardia, hypokalemia, myocardial ischemia, tachyphylaxis (> 72 hr); possible increased mortality with long-term use	Proarrhythmia, hypotension (avoid bolus), tachycardia, < 1% thrombocytopenia, possible increased mortality with long-term use
Other comments	Consider in severe hypotension	Consider if receiving a β-blocker or in those with high pulmonary artery pressures

AC = adenylate cyclase; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; CO = cardiac output; PDE = phosphodiesterase.

I. Vasopressin Antagonists
   1. Use is limited because of their significant cost and their limited effects on meaningful long-term ADHF outcomes.
      a. Should be viewed as "add on" therapy to aggressive diuresis and not as initial or adjunctive therapy for fluid removal
      b. Strict free water restriction is guideline recommended (expert opinion).
   2. Tolvaptan is FDA approved for clinically significant hyponatremia associated with HF.
      a. In those at risk of or having active cognitive symptoms despite water restriction (i.e., serum sodium less than 125 mEq/L)
      b. In those with less marked hyponatremia (i.e., less than 135 mEq/L) having neurologic symptoms and who have no correction with fluid restriction, including patients with HF and syndrome of inappropriate secretion of antidiuretic hormone)
   3. Clinical use:
      a. Oral dosing: 15 mg daily; then titrated to 30–60 mg as needed
      b. Pharmacology: Binds to and inhibits the V_2 receptor, located in the renal tubule where water reabsorption is regulated
         i. Exerts its clinical effect within 2–4 hours and lasts about 24 hours
         ii. Increases serum sodium by about 2–4 mEq/L within 12–24 hours
         iii. Increases net urinary output and reduces total body weight (1–2 kg)
      c. Initiate only in the hospital setting to allow monitoring of volume status and serum sodium concentrations.
      d. An overly rapid rise in serum sodium (maximum correction in any 24-hour period of chronic hyponatremia should be less than 9 mEq/L) can result in hypotension, hypovolemia, and neurologic sequelae.

e. Contraindicated with CYP3A4 inhibitors (tolvaptan is a substrate of 3A4) and in those with an eCrCl less than 10 mL/minute
f. The FDA warns against use beyond 30 days (i.e., hepatotoxicity).
g. Trials show effectiveness in correcting sodium with maintained therapy but no improvement in global clinical status or mortality and no reductions in rehospitalization.
    i. Role in long-term management of HF remains unclear.
    ii. Hyponatremia redevelops after therapy cessation.

Patient Case

Questions 5–7 pertain to the following case.

A 72-year-old man is admitted to the hospital for HF decompensation. The patient has progressively increased dyspnea when walking (now 10 ft [3 m], previously 30 ft [6 m]) and orthopnea (now four pillows, previously two pillows), increased bilateral lower-extremity swelling (3+), 13 kg of weight gain in the past 3 weeks, and dietary nonadherence. He has a history of idiopathic dilated cardiomyopathy (LVEF 25%, NYHA class III), paroxysmal AF, and hyperlipidemia. Pertinent laboratory values are as follows: BNP 2300 pg/mL (0–50 pg/mL), K^+ 4.9 mEq/L, BUN 32 mg/dL, SCr 2.0 mg/dL (baseline 1.9 mg/dL), aspartate aminotransferase (AST) 40 IU/L, alanine aminotransferase 42 IU/L, INR 1.3, aPTT 42 seconds, blood pressure 108/62 mm Hg, heart rate 82 beats/minute, and SaO_2 95%. Home medications include carvedilol 12.5 mg twice daily, lisinopril 40 mg/day, furosemide 80 mg twice daily, spironolactone 25 mg/day, and digoxin 0.125 mg/day.

5. Which regimen is best for treating his ADHF?
    A. Carvedilol 25 mg twice daily.
    B. Sodium nitroprusside 0.1 mcg/kg/min IV.
    C. Furosemide 120 mg intravenously twice daily.
    D. Milrinone 0.5 mcg/kg/minute.

6. After being initiated on intravenous loop diuretics with only minimal urinary output, the patient is transferred to the coronary care unit for further management of diuretic-refractory decompensated HF. His SaO_2 is now 87% on a 4-L nasal cannula, and an arterial blood gas is being obtained. His blood pressure is 110/75 mm Hg and heart rate is 75 beats/minute. The patient's SCr and K^+ concentrations have begun to rise and are now 2.7 mg/dL and 5.4 mmol/L, respectively. In addition to a one-time dose of intravenous chlorothiazide, which regimen is most appropriate for this patient?
    A. Nitroglycerin 20 mcg/minute.
    B. Sodium nitroprusside 0.3 mg/kg/minute.
    C. Dobutamine 5 mcg/kg/minute.
    D. Milrinone 0.5 mcg/kg/minute.

Patient Case *(Cont'd)*

7. The patient initially responds with 2 L of urinary output overnight, and his weight decreases by 1 kg the next day. However, by day 5, his urinary output has diminished again, and his SCr has risen to 4.3 mg/dL. He was drowsy and confused this morning during rounds. His extremities are cool and cyanotic, blood pressure is 89/58 mm Hg, and heart rate is 98 beats/minute. It is believed that he is no longer responding to his current regimen. A Swan-Ganz catheter is placed to determine further management. Hemodynamic values are cardiac index 1.5 L/minute/m^2, SVR 2650 dynes/second/cm^5, and PCWP 30 mm Hg. Which regimen is most appropriate for his current symptoms?
   A. Milrinone 0.2 mcg/kg/minute.
   B. Dobutamine 10 mcg/kg/minute.
   C. Sodium nitroprusside 0.1 mcg/kg/minute.
   D. Phenylephrine 20 mcg/minute.

III. ACUTE LIFE-THREATENING ARRHYTHMIAS

A. Adult Cardiac Arrest (Box 3)

Box 3. Select ACLS Algorithms[a]

1. Start CPR (give oxygen; attach monitor/defibrillator)
2. Rhythm shockable? (If yes, go to Pulseless VT/VF No. 3; if no, go to asystole/PEA No. 11)
Algorithm for Pulseless VT or VF
3. Defibrillation (shock 1)
4. CPR 2 min Establish IV/IO access[a]
5. Reassess rhythm; shock if appropriate and proceed If no sign of ROSC, go to Asystole/PEA algorithm If ROSC, initiate post–cardiac arrest care
6. Defibrillation (shock 2)
7. CPR 2 min Epinephrine 1 mg IV/IO every 3–5 min Consider advanced airway, capnography
Algorithm for Pulseless VT or VF
8. Reassess rhythm; shock if appropriate and proceed If no sign of ROSC, go to asystole/PEA algorithm If ROSC, initiate post–cardiac arrest care
9. Defibrillation (shock 3)
10. CPR 2 min Amiodarone[b] 300 mg IV/IO × 1; may repeat at 150-mg bolus × 1; lidocaine may also be considered[b] Reversible causes of the event should be identified and corrected[c]

Box 3. Select ACLS Algorithms[a] *(Cont'd)*

Algorithm for Asystole or PEA
11. CPR 2 min Establish IV/IO access[a] Epinephrine 1 mg IV/IO every 3–5 min Consider advanced airway, capnography
12. Reassess rhythm; shock if appropriate and proceed to No. 6 or 7 for pulseless VT/VF If no sign of ROSC, proceed
13. CPR 2 min Treat reversible causes[c]
14. Reassess rhythm; shock if appropriate and proceed to No. 6 or 7 for pulseless VT/VF If no sign of ROSC, continue steps 11–14 If ROSC, initiate post–cardiac arrest care

[a]If no IV/IO access, endotracheal administration of epinephrine, lidocaine, and atropine is allowed at 2–2.5 times the recommended IV/IO dose. Dilute this dose with 5–10 mL of sterile water or normal saline.

[b]If amiodarone is unavailable, lidocaine may be considered. Lidocaine 1–1.5 mg/kg IV, repeat 0.5–0.75 mg/kg IV/IO every 5–10 min (maximum 3 mg/kg). Lidocaine has not been shown to improve ROSC and hospital admission compared with amiodarone.

[c]Hypovolemia, hypoxia, hydrogen ion (acidosis), hypokalemia or hyperkalemia, hypothermia, tension pneumothorax, tamponade (cardiac), toxins, thrombosis (pulmonary), thrombosis (coronary).

ACLS = advanced cardiac life support; CPR = cardiopulmonary resuscitation; IO = intraosseous(ly); PEA = pulseless electrical activity; ROSC = return of spontaneous circulation; VF = ventricular fibrillation; VT = ventricular tachycardia.

B. Targeted Temperature Management (TTM) after cardiac arrest
    1. Indicated in adult patients who are comatose in whom return of spontaneous circulation (ROSC) has been achieved after cardiac arrest
        a. Improves neurologic outcomes after ROSC
        b. Optimal benefit for those in whom cooling begins soon after arrest
    2. Cooling process
        a. Goal temperature: 32°C–36°C
        b. Duration: At least 24 hours after achieving the goal temperature
        c. Slowly rewarmed at a typical rate of 0.3°C/hour until core body temperature is reached
    3. Pharmacologic therapy during TTM
        a. Shivering
            i. Occurs when body temperature drops below 36°C and diminishes below 34°C
            ii. Shivering increases heat production by 600% and increases oxygen consumption and is not desirable.
            iii. Agents used to reduce shivering include meperidine, buspirone, clonidine, dexmedetomidine, and neuromuscular blocking agents.
        b. Sedation
            i. Required to minimize pain or anxiety
            ii. Agents used to provide sedation include the combination of fentanyl, midazolam, or propofol.

c. Other adverse effects related to hypothermia
    i. Bradycardia – Lower heart rates are associated with improved outcomes; therefore, no aggressive correction is required.
    ii. Electrolyte abnormalities
        (a) Magnesium – Maintain serum magnesium concentrations at normal to high range.
        (b) Potassium – Hypokalemia is common during the hypothermic phase, whereas hyperkalemia occurs during rewarming; avoid aggressive supplementation during hypothermia.
    iii. Bleeding
        (a) Increased risk because of impaired platelet function, reduced number of platelets, impaired production of clotting enzymes, etc.
        (b) Monitor prothrombin time and aPTT once the temperature falls below 37°C.
    iv. Arrhythmias
        (a) If life-threatening arrhythmias occur during hypothermia, cooling should be discontinued.
        (b) Treatment of life-threatening arrhythmias should generally follow advanced cardiac life support (ACLS) principles.
    v. Hyperglycemia
        (a) Hypothermia decreases insulin sensitivity and insulin secretion from the pancreas.
        (b) Maintain blood glucose concentrations of 140–180 mg/dL during TTM.
    vi. Hypotension
        (a) Many patients require blood pressure support, and during TTM, a MAP above 80 mm Hg is preferred.
        (b) Choice of vasoactive agents depends on patient heart rate, SBP, and risk of arrhythmias.
    vii. Monitor for infection and hepatic impairment, and use adjunctive treatments as necessary.

C. Symptomatic Bradycardia
    1. If unstable, atropine 0.5 mg every 3–5 minutes (maximum dose 3 mg). (Note: Unstable = hypotension, acutely altered mental status, signs of shock, ischemic chest discomfort, acute HF)
    2. If atropine fails, transcutaneous pacing, dopamine 2–10 mcg/kg/minute, or epinephrine 2–10 mcg/minute

D. Symptomatic Tachycardia
    1. If unstable, synchronized cardioversion
    2. If stable, determine whether the QRS complex is narrow or wide.
        a. Narrow-complex tachycardia (QRS less than 120 milliseconds); usually atrial arrhythmias
            i. Regular ventricular rhythm: Supraventricular tachycardia (SVT) or sinus tachycardia likely
                (a) Vagal maneuvers or adenosine 6-mg intravenous push, followed by a 20-mL saline flush, then a 12-mg intravenous push (may repeat once)
                    (1) Rapid push followed by elevation of arm to increase circulation
                    (2) Larger doses may be needed in patients taking theophylline or caffeine.
                    (3) Initial dose should be reduced to 3 mg in patients taking dipyridamole or carbamazepine and in patients after heart transplantation, and when the drug is being given by central access.
                    (4) Use adenosine cautiously in severe CAD.
                    (5) Adenosine should not be given to patients with asthma.
                    (6) Do not give adenosine for unstable or for irregular or polymorphic wide-complex tachycardias because it can cause degeneration to ventricular fibrillation (VF).

(b) If vagal maneuvers or adenosine fails to convert paroxysmal SVT, calcium channel blockers (CCBs) or β-blockers can be used. If Wolff-Parkinson-White syndrome, avoid verapamil, diltiazem, and digoxin

ii. Irregular (narrow complex) ventricular rhythm: AF (or possibly atrial flutter)

(a) General management should focus on control of the rapid ventricular rate.

(1) Usually non-dihydropyridine CCBs (diltiazem, verapamil) or β-blockers; digoxin sometimes useful

(2) Rate is acceptable if it is less than 110 beats/minute at rest in asymptomatic persistent AF.

(b) If the patient is hemodynamically unstable, synchronized cardioversion is recommended.

(c) Patients with AF for more than 48 hours are at high risk of cardioembolic events and should not be immediately cardioverted, if stable.

(d) Transesophageal echocardiography before cardioversion is an alternative strategy to ensure the absence of left atrial clot.

(e) Risk of thromboembolic event surrounding cardioversion (both pharmacologic and electrical) is greatest within the first 10 days.

(f) Cardioversion

(1) If AF for up to 7 days, either elective direct current conversion or chemical cardioversion

(A) Flecainide, dofetilide, propafenone, ibutilide, or amiodarone (proven efficacy)

(B) Digoxin and sotalol are not recommended and may be harmful.

(C) Disopyramide, quinidine, and procainamide are less effective or incompletely studied.

(2) If AF lasts greater than 7 days, administer either elective direct current conversion or chemical cardioversion with dofetilide, amiodarone, or ibutilide (proven efficacy).

b. Wide-complex tachycardia (QRS greater than 120 milliseconds): Usually ventricular arrhythmias

i. VT or unknown mechanism

(a) Consider adenosine only if regular and monomorphic.

(b) Intravenous procainamide, amiodarone (or sotalol); lidocaine second line

(c) Avoid procainamide and sotalol if prolonged QTc.

ii. Definite SVT with aberrancy: Probably transiently slowed or converted by adenosine

iii. Polymorphic (irregular) VT

(a) Induced primarily when the QTc interval is greater than 500 milliseconds (torsades de pointes)

(b) If unstable, polymorphic (irregular) VT requires immediate defibrillation with the same strategy as VF.

(c) If stable, intravenous magnesium 1- to 2-g intravenous bolus (maximum 16 g every 24 hours) may be given; however, this is supported only by observational studies in the setting of wide QRS.

(d) Withdrawal of QT-prolonging medications, correction of low magnesium or K^+ concentrations

(1) Class I and III antiarrhythmic drugs (AADs)

(2) Assess for drug interactions by CYP3A4 (e.g., azole antifungals, erythromycin).

(3) Assess for other QTc-prolonging drugs (e.g., haloperidol, ziprasidone, droperidol, promethazine, macrolide and quinolone antibiotics, tricyclic antidepressants, or drugs contraindicated with dofetilide such as sulfamethoxazole/trimethoprim or thiazides).

E. AAD Overview (Tables 19 and 20)

Table 19. Vaughan-Williams AAD Classes

Class/Ion Affected	Agents	Physiologic Effect	Result on Electrophysiologic Parameters	Clinical Utility
Class I/Na^+ channel blockers				
Ia (intermediate)	Disopyramide quinidine, procainamide	↓ Conduction velocity; ↑ refractory period	↑ QRS complex and ↑ QT interval	Atrial and ventricular arrhythmias
Ib (fast)	Lidocaine, mexiletine, phenytoin	↓ Conduction velocity; ↓↑ refractory period	↓ QT interval	Ventricular arrhythmias
Ic (slow)	Flecainide, propafenone	↓↓↓ Conduction velocity; Ø refractory period	↑ QRS complex	Supraventricular arrhythmias and ventricular arrhythmias
Class II β-Blockers	Metoprolol, esmolol, atenolol	↓ Conduction velocity; ↑ refractory period	↓ HR and ↑ PR interval	Atrial and ventricular arrhythmias
Class III K^+ channel blockers	Amiodarone,[a] dronedarone,[a] sotalol,[b] dofetilide, ibutilide	Ø Conduction velocity; ↑↑↑ refractory period	↑ QT interval	Atrial and ventricular arrhythmias
Class IV $Ca2^+$ channel blockers	Diltiazem, verapamil	↓ Conduction velocity; ↑ refractory period	↓ HR and ↑ PR interval	Atrial and ventricular arrhythmias

[a]Amiodarone and dronedarone have Ib, II, and IV class activity in addition to class III actions.

[b]Sotalol has 50%/50% β-blocking properties/K^+-blocking properties.

AAD = antiarrhythmic drug; $Ca2^+$ = calcium; HR = heart rate; Na^+ = sodium. ↑ = increases; ↓ = decreases; Ø = no effect.

Table 20. AAD Properties and Dosing (class I and III agents only)

Drug	AEs, Contraindications, PK, and Drug Interactions	Dosing by Indication
Class Ia: Na^+ channel blockers		
Quinidine (Quinidex, Quinaglute)	AEs: Nausea, vomiting, and diarrhea (30%), "cinchonism" (CNS and GI symptoms, tinnitus), strong vagolytic and anticholinergic properties, TdP (first 72 hr), hypotension, GI upset PK: Half-life 5–9 hr Potent inhibitor of CYP2D6; substrate and inhibitor of CYP3A4 DIs: Warfarin, digoxin	AF conversion: Avoid use because of GI AEs AF and VT maintenance: Sulfate: 200–400 mg PO every 6 hr Gluconate (CR): 324 mg PO every 8–12 hr Decrease dose by 25% if CrCl < 10 mL/min
Procainamide (Pronestyl)	AEs: Hypotension (IV use, 5%), TdP CI: LVEF < 40% PK: Active metabolite NAPA (class III effects) may accumulate in renal dysfunction	AF conversion: 1 g IV for 30 min; then 2 mg/min (1-hr efficacy 51%) AF maintenance: No oral agent available VT conversion: 20 mg/min IV until 17 mg/kg, arrhythmia ceases, hypotension, or QRS widens > 50% VT maintenance: 1–4 mg/min Reduce dose in renal and liver dysfunction

Table 20. AAD Properties and Dosing (class I and III agents only) *(Cont'd)*

Drug	AEs, Contraindications, PK, and Drug Interactions	Dosing by Indication
Class Ia: Na^+ channel blockers		
Disopyramide (Norpace, Norpace CR)	AEs: Anticholinergic effects, TdP, ADHF (potent negative inotropic effect) CIs: Cardiogenic shock, congenital long QT syndrome, second- or third-degree AVB, glaucoma PK: Half-life 4–8 hr Substrate of CYP2D6 DI: May enhance the effect of β-blockers	AF conversion: IR 200 mg (if < 50 kg) or 300 mg (if > 50 kg) PO every 6 hr AF maintenance: 400–800 mg/day in divided doses (recommended adult dose 600 mg/day given as IR 150 mg PO every 6 hr or as CR 300 mg PO every 12 hr) If < 50 kg, moderate renal dysfunction (CrCl > 40 mL/min) or hepatic dysfunction, max 400 mg/day If severe renal dysfunction (IR only; avoid CR) CrCl 30–40 mL/min, 100 mg every 8 hr CrCl 15–30 mL/min, 100 mg every 12 hr CrCl < 15 mL/min, 100 mg every 24 hr VTs: Use has fallen out of favor because of the availability of newer agents with less toxicity
Class Ib: Na^+ channel blockers		
Lidocaine (Xylocaine)	AEs: CNS (perioral numbness, seizures, confusion, blurry vision, tinnitus) CI: Third-degree AVB PK: Reduce dose in those with HF, liver disease, low body weight, and renal dysfunction and in older adults DI: Amiodarone (increased lidocaine concentrations)	Pulseless VT/VF conversion or VT with a pulse: 1–1.5 mg/kg IVP; repeat 0.5–0.75 mg/kg every 3–5 min (max 3 mg/kg) (If LVEF < 40%, 0.5–0.75 mg/kg IVP) (Amiodarone DOC in pulseless VT/VF; lidocaine acceptable if amiodarone not available) VT maintenance: 1–4 mg/min Reduce maintenance infusion in liver disease
Mexiletine (Mexitil)	AEs: CNS (tremor, dizziness, ataxia, nystagmus) CI: Third-degree AVB PK: Half-life 12–20 hr Substrate CYP2D6, CYP1A2 Inhibitor CYP1A2	VT maintenance: 200–300 mg PO every 8 hr; max 1200 mg/day Reduce dose by 25%–30% in hepatic impairment
Class Ic: Na^+ channel blockers (Note: Avoid in patients with HF or after MI; increased risk of sudden death)		
Propafenone[a] (Rythmol, Rythmol SR)	AEs: Metallic taste, dizziness, ADHF, bronchospasm, bradycardia, heart block (negative inotropy and β-blocking properties) CIs: HF (NYHA III–IV), liver disease, valvular disease (TdP), CAD, MI PK: Half-life 10–25 hr Substrate CYP2D6, CYP1A2, CYP3A4 Inhibitor CYP1A2, CYP2D6 DIs: Digoxin ↑ by 70%; warfarin ↑ by 50% as well as drugs that inhibit CYP 2D6, 1A2, 3A4 (increased propafenone)	AF conversion: 600 mg PO × 1 (efficacy 45% at 3 hr) 450 mg PO × 1 (weight < 70 kg) AF maintenance: HCl: 150–300 mg PO every 8–12 hr HCl (SR): 225–425 mg PO every 12 hr Reduce dose 70%–80% in hepatic impairment
Flecainide[a] (Tambocor)	AEs: Dizziness, tremor, ADHF (negative inotropy), vagolytic, anticholinergic, hypotension CIs: HF, CAD, valvular disease, LVH (TdP) PK: Half-life 10–20 hr Substrate CYP2D6, CYP1A2 Inhibitor CYP2D6 DI: Digoxin ↑ by 25%	AF conversion: 300 mg PO × 1 (efficacy 50% at 3 hr) AF maintenance: 50–150 mg PO BID Reduce dose by 50% when CrCl < 35 mL/min

Table 20. AAD Properties and Dosing (class I and III agents only) *(Cont'd)*

Drug	AEs, Contraindications, PK, and Drug Interactions	Dosing by Indication
Class III: K^+ channel blockers		
Amiodarone (Cordarone)	AEs: Pulmonary fibrosis 3%–17%, hyperthyroidism 3%, hypothyroidism 30%, neurologic toxicity 20%–40%, GI upset, photosensitivity, corneal deposits, hepatitis, blue-gray skin 15%, TdP < 1%, heart block 14%, hypotension (IV), phlebitis (IV; $Ca2^+$- and β-blocking properties), bradycardia CIs: Iodine hypersensitivity, hyperthyroidism, third-degree AV heart block PK: Half-life 58 days (avg) Inhibits CYP3A4/2D6/2C9/1A2/2C19 and intestinal P-gp Substrate CYP3A4/1A2/2C19/2D6 DIs: Warfarin, digoxin, statins (max simvastatin dose 20 mg/day), phenytoin ↑ ≥ 50%, lidocaine, and others Does not increase mortality in patients with HF	AF conversion: IV: 5–7 mg/kg IV over 30–60 min, then 1.2–1.8 g/day continuous IV or divided oral doses until 10 g PO: 1.2–1.8 g/day in divided doses until 10 g AF maintenance: 200–400 mg/day PO Pulseless VT/VF conversion: 300 mg or 5 mg/kg IVB in 20 mL of D_5W or NS; repeat 150 mg IVB every 3–5 min Stable VT: 150 mg IVB in 100 mL of D_5W for 10 min VT/VF maintenance: 1 mg/min × 6 hr, then 0.5 mg/min (max 2.2 g/day)
Sotalol (Betapace, Betapace AF)	AEs: ADHF, bradycardia, AVB, wheezing, 3%–8% TdP within 3 days of initiation, bronchospasm (β-blocking effects) CIs: Baseline QTc > 440 ms or CrCl < 40 mL/min (AF only), LVEF < 40% PK: Renally eliminated, half-life 30–40 hr Hospitalization ideal for initiation of therapy because of BW: Do not initiate if baseline QTc interval > 450 ms; if QTc > 500 ms during therapy, reduce the dose, prolong the infusion duration, or d/c use Not effective for AF conversion	AF maintenance (based on CrCl): 80 mg PO BID (> 60 mL/min) 80 mg PO daily (40–60 mL/min) CI < 40 mL/min VT maintenance (based on CrCl): 80 mg PO BID (> 60 mL/min) 80 mg PO daily (30–60 mL/min) 80 mg PO every 36–48 hr (10–30 mL/min) 80 mg PO: Individualize; every 48 hr minimum (< 10 mL/min)
Dofetilide (Tikosyn)	AEs: TdP (0.8%; 4% if no renal adjustment), diarrhea CIs: Baseline QTc > 440 ms or CrCl < 20 mL/min PK: Renal and hepatic elimination Half-life 6–10 hr Substrate CYP3A4 DIs: CYP3A4 inhibitors and drugs secreted by kidney (cimetidine, ketoconazole, verapamil, trimethoprim, prochlorperazine, megestrol), HCTZ BW: Hospitalization mandatory for initiation, obtain QTc 2–3 hr after each of the first five doses, reduce 50% if QTc ↑ > 15%; NTE QTc > 500 ms Does not increase mortality in patients with HF	AF conversion (based on CrCl; efficacy 12% at 1 mo): 500 mcg PO BID (> 60 mL/min) 250 mcg PO BID (40–60 mL/min) 125 mcg PO BID (20–40 mL/min) CI < 20 mL/min AF maintenance: Dose as above according to renal function; adjust for QTc NTE 500 ms or > 15% ↑ in QTc

Table 20. AAD Properties and Dosing (class I and III agents only) *(Cont'd)*

Drug	AEs, Contraindications, PK, and Drug Interactions	Dosing by Indication
Class III: K^+ channel blockers		
Ibutilide (Corvert)	AEs: TdP 8%, AV heart block (β-blocking properties) CIs: Baseline QTc > 440 ms, LVEF < 30%, concomitant AADs PK: Half-life 2–12 hr (avg 6) DIs: CYP3A4 inhibitors or QT-prolonging drugs ECG monitoring during and 4 hr after DCC	AF conversion: 1 mg IV (≥ 60 kg) or 0.01 mg/kg IV (< 60 kg); repeat in 10 min if ineffective (efficacy 47% at 90 min) BW: Potentially fatal arrhythmias (e.g., polymorphic VT) can occur with ibutilide, usually in association with TdP; patients with chronic AF may not be the best candidates for ibutilide conversion
Dronedarone (Multaq)	AEs: Worsening HF, QT prolongation, hypokalemia or hypomagnesemia with K^+-sparing diuretics, hepatic failure CIs: QTc ≥ 500 ms or PR ≥ 280 ms, NYHA class IV HF or NYHA class II–III HF with recent ADHF, severe hepatic impairment, second- or third-degree AVB, or HR < 50 beats/min PK: Half-life 13–19 hr Substrate 3A4 Inhibitor intestinal P-gp DIs: CYP3A4 inhibitors, QT-prolonging drugs, simvastatin, tacrolimus/sirolimus, warfarin, and other CYP3A4 substrates with narrow therapeutic range, digoxin and other P-gp substrates (dabigatran, rivaroxaban)	AF maintenance: 400 mg orally BID d/c if QTc ≥ 500 ms BW: Risk of death is doubled when used in patients with symptomatic HF with recent decompensation necessitating hospitalization or NYHA class IV symptoms; use is contraindicated in these patients Use in patients with permanent AF doubles the risk of death, stroke, and hospitalization for HF; use is contraindicated in patients with AF who will not or cannot be converted to normal sinus rhythm

[a]Indicates that pill-in-pocket approach can be used for selected patients.

AV = atrioventricular; AVB = atrioventricular block; CAD = coronary artery disease; CI = contraindication; CNS = central nervous system; CR = controlled release; d/c = discontinue; DCC = direct current cardioversion; D_5W = dextrose 5%; DI = drug interaction; DOC = drug of choice; HCl = hydrochloride; HCTZ = hydrochlorothiazide; HR = heart rate; IR = immediate release; LVH = left ventricular hypertrophy; ms = millisecond(s); NAPA = *N*-acetylprocainamide; NS = normal saline; NTE = not to exceed; NYHA = New York Heart Association; PK = pharmacokinetics; QTc = corrected QT interval; SR = sustained release; TdP = torsades de pointes; VF = ventricular fibrillation; VT = ventricular tachycardia.

F. Long-term Management of Ventricular Arrhythmias
   1. Nonsustained VT
      a. Asymptomatic
         i. Infrequent ventricular ectopic beats, couplets, and triplets without other signs of underlying structural heart disease (SHD) or inherited arrhythmia syndrome should be considered a normal variant in asymptomatic patients.
         ii. No treatment other than reassurance is needed for patients without SHD or inherited arrhythmia disorder.
         iii. Treat survivors of MI and HFrEF with β-blockers (class I), unless contraindicated.
      b. Symptomatic
         i. β-Blockers may be considered for a therapeutic trial in symptomatic patients (class IIb, level of evidence [LOE] C).
         ii. Non-dihydropyridine CCBs may be considered as an alternative to β-blocker therapy in suitable patients without SHD.

iii. AAD therapy (amiodarone, flecainide, mexiletine, propafenone, sotalol) may be considered to improve symptoms associated with arrhythmias in patients receiving adequate doses of a β-blocker or CCB (class IIb; LOE C).
   (a) Flecainide and propafenone are not recommended to suppress premature ventricular contractions in patients with reduced LV function (class III).
   (b) Sotalol should be used with caution in patients with chronic kidney disease and should be avoided in patients with a prolonged QT interval at baseline or excessive prolongation of QT interval (500 milliseconds) on therapy initiation (class I; LOE B).
   (c) Amiodarone appears to have less overall proarrhythmic risk than other AADs in patients with HF and may be preferred to other membrane-active AADs unless a functioning defibrillator has been implanted (class IIb; LOE C).
iv. Amiodarone, sotalol, and other β-blockers are useful after defibrillator implantation to reduce shocks and suppress nonsustained VT in patients who are unsuitable for ICD therapy, in addition to optimal medical therapy for patients with HF.

2. Sustained VT
   a. Immediate defibrillation (ACLS management)
   b. Evaluate cardiac structure and function.
   c. ICDs indicated for most patients with SHD

G. Implantable Cardioverter-Defibrillators
1. For primary prevention of SCD
   a. Previous MI, at least 40 days earlier, and EF of 35% or less
   b. Nonischemic dilated cardiomyopathy, LVEF of 35% or less receiving optimal chronic medications for at least 3 months
   c. Syncope with SHD and inducible VT/VF during electrophysiologic study
   d. High risk of life-threatening VT/VF; congenital long QT syndrome with recurrent symptoms or torsades de pointes while receiving a β-blocker
   e. Must have reasonable survival expectation for more than 1 year
2. For secondary prevention of SCD
   a. Previous episode of resuscitated VT/VF, hemodynamically unstable VT with no completely reversible cause, or sustained VT in presence of heart disease
   b. Must be receiving optimal chronic medications (β-blockers, ACE inhibitors)
   c. Must have reasonable survival expectation for more than 1 year
3. General medication considerations with ICD (Table 21)
   a. β-Blockers
      i. Considered mainstay therapy
      ii. Effective in suppressing ventricular ectopic beats and in reducing SCD in a spectrum of cardiac disorders in patients with and without HF (nonsustained VT)
   b. Amiodarone
      i. No better than ICD in reducing SCD as a lone agent; no mortality benefit
      ii. Can be used to treat symptomatic nonsustained VT if β-blockers not effective when ICD not indicated
      iii. Can be used in combination with β-blockers to decrease firing of ICD (defibrillator storm)
   c. Sotalol
      i. No mortality advantage
      ii. Can suppress VT and be used to decrease frequency of ICD firing
      iii. Greater proarrhythmic potential; avoid in patients with severely depressed LVEF or significant HF; renal dosing necessary

Table 21. Alteration of Defibrillation Threshold

Threshold Alteration	Medications	Comments
Increase threshold	Amiodarone, lidocaine, and mexiletine	Reprogram ICD, increased energy (joules) needed
Decrease threshold	Sotalol	May decrease energy needed for DCC

ICD = implantable cardioverter-defibrillator.

H. Treatment of Arrhythmias in Special Patient Populations
   1. Heart failure
      a. Avoid class Ia and class Ic agents.
      b. Amiodarone and dofetilide (used for atrial arrhythmias only) have a neutral effect on mortality in patients with LV dysfunction after an MI.
      c. Dronedarone (used in atrial arrhythmias only) is contraindicated in patients with symptomatic HF with recent decompensation necessitating hospitalization or NYHA class IV symptoms; risk of death was doubled in these patients.
   2. Acute MI
      a. Avoid class Ia and class Ic agents.
      b. CAST trial with class Ic agents (encainide, flecainide) showed greater mortality when used to treat post-MI non–life-threatening ventricular arrhythmias; avoid class Ic agents in patients with SHD.
      c. Class Ia medications: Increased mortality in MI survivors
      d. Amiodarone and dofetilide (used for atrial arrhythmias only) have a neutral effect on mortality in patients with LV dysfunction after an MI.

I. Drug-Induced Arrhythmias: Review all potential drug etiologies and treat appropriately.
   1. Drug-induced QT prolongation
      a. Discontinue offending agent if QT prolongation is significant (i.e., greater than 450 milliseconds).
      b. Ensure proper renal and hepatic dosing adjustments.
      c. Review electrolyte abnormalities and thyroid function tests.
      d. Ensure that all electrolytes are maintained at critical concentrations: K^+ greater than 4 mmol/L and less than 5 mmol/L and magnesium greater than 2 mg/dL.
      e. Ensure that all ECG parameters are within normal limits (e.g., QT interval less than 500 milliseconds).
   2. Drug-induced bradycardia or atrioventricular block
      a. β-Blocker, CCB, digoxin
      b. Administer antidote, if appropriate (e.g., calcium for CCB toxicity).
   3. Review for drug interactions. AADs have drug interactions that may cause significant outcomes.

Patient Cases

Questions 8 and 9 pertain to the following case.

A 68-year-old man is admitted after an episode of syncope, with a presyncopal syndrome of seeing black spots and dizziness before passing out. Telemetry monitor showed sustained VT for 45 seconds. His medical history includes HF NYHA class III, LVEF 30%, two MIs, hypertension for 20 years, LV hypertrophy, DM, and diabetic nephropathy. His medications include lisinopril 5 mg/day, furosemide 20 mg twice daily, metoprolol 25 mg twice daily, digoxin 0.125 mg/day, glyburide 5 mg/day, atorvastatin 40 mg, and aspirin 81 mg/day. His blood pressure is 120/75 mm Hg, with heart rate 80 beats/minute, BUN 30 mg/dL, and SCr 2.2 mg/dL.

8. Which is the best therapy to initiate for conversion of his sustained VT?
   A. Amiodarone 150 mg intravenously for 10 minutes, then 1 mg/minute for 6 hours, then 0.5 mg/minute.
   B. Sotalol 80 mg twice daily titrated to QTc of about 450 milliseconds.
   C. Dofetilide 500 mcg twice daily titrated to QTc of about 450 milliseconds.
   D. Procainamide 20 mg/minute, with a maximum of 17 mg/kg.

9. The patient presents to the ED 3 months after amiodarone maintenance initiation (he refused ICD placement) after a syncopal episode, during which he lost consciousness for 30 seconds, according to witnesses. He also has rapid heart rate episodes during which he feels dizzy and lightheaded. He feels very warm all the time (he wears shorts, even though it is winter), cannot sleep, and has lost 3 kg in weight. He received a diagnosis of hyperthyroidism caused by amiodarone therapy. On telemetry, he has runs of nonsustained VT. Which best predicts the duration of amiodarone-associated hyperthyroidism in this patient?
   A. Never.
   B. 1 month.
   C. 6 months.
   D. 18 months.

10. A 64-year-old woman presents to the ED with the chief concern of palpitations. Her medical history includes hypertension controlled with a diuretic and an inferior-wall MI 6 months ago. She is pale and diaphoretic but can respond to commands. The patient's laboratory values are within normal limits. Her vital signs include blood pressure 95/70 mm Hg and heart rate 145 beats/minute; telemetry shows sustained VT. Although initially unresponsive to β-blockers, the patient is successfully treated with lidocaine. Subsequent electrophysiologic testing reveals inducible VT, and sotalol 80 mg orally twice daily is prescribed. Two hours after the second dose, the patient's QTc is 520 milliseconds. Which regimen change would be most appropriate for this patient?
   A. Continue sotalol at 80 mg orally twice daily.
   B. Increase sotalol to 120 mg orally twice daily.
   C. Discontinue sotalol and initiate dofetilide 125 mcg orally twice daily.
   D. Discontinue sotalol and initiate amiodarone 400 mg orally three times daily.

IV. HYPERTENSIVE CRISES

A. Definitions
   1. Hypertensive emergency
      a. Severe elevations in blood pressure (usually greater than 180/120 mm Hg) with evidence of new or worsening target-organ damage
      b. Acute target-organ damage can include hypertensive encephalopathy, intracranial hemorrhage, acute ischemic stroke, or other acute neurologic deficit; UA or acute MI; acute LV failure with pulmonary edema; dissecting aortic aneurysm; retinopathy or papilledema; decreased urinary output or acute renal failure; eclampsia
      c. Actual blood pressure may not be as important as the rate of blood pressure rise.
      d. Requires immediate blood pressure lowering (not necessarily to normal ranges) to prevent or limit further target-organ damage
      e. In general, oral therapy is discouraged for hypertensive emergencies.
   2. Hypertensive urgency
      a. Situations associated with severe blood pressure elevation in otherwise stable patients without acute or impending change in target-organ damage or dysfunction
      b. Short-term risk is not as high; therefore, blood pressure reduction occurs over several days, not immediately.

B. Goals and Treatment
   1. Hypertensive emergency
      a. Goal is to minimize target-organ damage safely by rapid recognition of the problem and early initiation of appropriate antihypertensive treatment.
      b. Patients are usually admitted for intensive care unit care and close follow-up.
      c. Lower MAP by no more than 25% in the first hour; then reduce SBP to 160 mm Hg and DBP to 100–110 mm Hg over next 2–6 hours; then to normal over next 24–48 hours
      d. Exceptions:
         i. Do not lower blood pressure in acute ischemic stroke unless greater than 220/120 mm Hg or greater than 185/110 mm Hg in tissue plasminogen activator candidates.
         ii. Rapidly lower blood pressure to less than 140 mm Hg in the first hour of treatment in severe preeclampsia or eclampsia and in pheochromocytoma with hypertensive crisis.
         iii. Rapidly lower blood pressure to less than 120 mm Hg in the first hour of treatment in aortic dissection.
      e. Intravenous medications used commonly (Table 22)
      f. No randomized evidence to suggest one drug of choice because of small trial size, lack of long-term follow-up, and failure to report outcomes
      g. Two trials have shown that nicardipine is better than labetalol in achieving the short-term blood pressure target.
      h. Agents are chosen on the basis of drug pharmacology, pathophysiologic factors underlying the patient's hypertension, degree of progression of target-organ damage, desirable rate of blood pressure decline, and presence of patient characteristics (Tables 22 and 23).
      i. No randomized evidence exists comparing different strategies to reduce blood pressure, except in patients with intracranial hemorrhage.
      j. No randomized evidence suggests how rapidly to reduce blood pressure.
      k. Clinical experience indicates that excessive reductions in blood pressure can cause renal, cerebral, or coronary ischemia and should be avoided.

2. Hypertensive urgency
   a. Treated by reinstitution or intensification of antihypertensive drug therapy
   b. No indication for referral to the ED, immediate reduction in blood pressure in the ED, or hospitalization
   c. No proven benefit exists from rapid reductions in blood pressure.
   d. Choice of agent used in this setting varies, and in many cases, adjusting chronic oral therapy (increasing doses), reinitiating therapy in the nonadherent, or adding a new agent (i.e., diuretic) to long-term therapy is appropriate.
   e. All patients with hypertensive urgency should be reevaluated within 7 days (preferably after 1–3 days).

C. Treatment Options (Table 22)

Table 22. Commonly Used IV Drugs for Hypertensive Emergencies

Drug (onset, duration)	IV Dose	Comments/AEs
Vasodilators		
Sodium nitroprusside (Nipride) (immediate, 2–3 min)	0.3–0.5 mcg/kg/min, increase in increments of 0.5 mcg/kg/min to achieve BP target; max 10 mcg/kg/min; for infusion rates ≥ 4–10 mcg/kg/min or duration > 30 min, thiosulfate can be coadministered to prevent cyanide toxicity	Intra-arterial BP monitoring recommended to prevent "overshoot"; lower doses required in older adult patients; tachyphylaxis common with extended use AEs: Cyanide or thiocyanate toxicity with prolonged use can result in irreversible neurologic changes and cardiac arrest, nausea, vomiting, methemoglobinemia CIs: Renal, hepatic failure Caution: Elevated ICP
Nitroglycerin (2–5 min, 5–10 min)	5–10 mcg/min, increase in increments of 5 mcg/min every 3–5 min to a max 20 mcg/min	Use only in patients with ACS and/or acute pulmonary edema; do not use in volume-depleted patients AEs: Headache, nausea, vomiting, tachyphylaxis
Hydralazine (Apresoline) (10 min, 1–4 hr)	5–10 mg by slow IV infusion every 4–6 hr (NTE initial 20 mg/dose)	BP begins to decrease within 10–30 min, and lasts 2–4 hr; unpredictability of response and prolonged duration of action make hydralazine less desirable first agent AEs: Reflex tachycardia, headache, flushing Caution: Angina or MI, elevated ICP, aortic dissection
Enalaprilat (Vasotec) (within 30 min, 12–24 hr)	0.625–1.25 mg over 5 min; doses can be increased up to max 5 mg every 6 hr	Should not be used in acute MI; mainly useful in hypertensive emergencies associated with high plasma renin activity; dose not easily adjusted; relatively slow onset (15 min) and unpredictability of BP response AEs: Renal insufficiency or failure, hyperkalemia CIs: Pregnancy, bilateral renal artery stenosis, angioedema (Note: Long half-life)

Table 22. Commonly Used IV Drugs for Hypertensive Emergencies *(Cont'd)*

Drug (onset, duration)	IV Dose	Comments/AEs
Vasodilators		
Fenoldopam (Corlopam) (< 5 min, 30 min)	0.1–0.3 mcg/kg/min, increased by 0.05–0.1 mcg/kg/min every 15 min to a max of 1.6 mcg/kg/min	Contraindicated in patients at risk of increased intraocular pressure (glaucoma) or ICP and those with sulfite allergy AEs: Headache, flushing, tachycardia, cerebral ischemia
Nicardipine (Cardene) (1–5 min, 15–30 min; up to 4 hr if prolonged infusion)	5 mg/hr, increased by 2.5 mg/hr every 5 min to a max 15 mg/hr	Contraindicated in advanced aortic stenosis; no dose adjustment needed for older patients AEs: Reflex tachycardia, nausea, vomiting, headache, flushing Caution: Angina or MI, acute HF
Clevidipine (Cleviprex) (2–4 min, 5–15 min)	1–2 mg/hr, doubling every 90 s until BP approaches target, then increasing by less than double every 5–10 min; max 32 mg/hr; max duration 72 hr	Patients with renal failure and hepatic failure and older adults not specifically studied – use low-end range for older adults; contraindicated in soy or egg product allergy, severe aortic stenosis, defective lipid metabolism (e.g., pathologic hyperlipidemia, lipoid nephrosis, or acute pancreatitis) Caution: HF, concomitant β-blocker use, reflex tachycardia, rebound HTN
Adrenergic Inhibitors		
Esmolol (Brevibloc) (1–2 min, 10–30 min)	LD 500–1000 mcg/kg IVB over 1 min, then a 50-mcg/kg/min infusion; for additional BP lowering, the bolus dose is repeated, and the infusion is increased in 50-mcg/kg/min increments as needed to a max 200 mcg/kg/min	Contraindicated in patients with concurrent β-blocker therapy, bradycardia, or decompensated HF AEs: Bronchospasm, HF exacerbation, bradycardia or heart block Caution: May worsen acute HF, asthma (higher doses may block β2-receptors and affect lung function in reactive airway disease), heart block
Labetalol (Normodyne, Trandate) (5–10 min, 3–6 hr)	20–80 mg every 15 min or initial 0.3–1 mg/kg dose (max 20 mg) slow IV injection every 10 min or 0.4–1.0 mg/kg/hr infusion up to max 3 mg/kg/hr	Contraindicated in reactive airway disease or chronic obstructive pulmonary disease; especially useful in hyperadrenergic syndromes; may worsen HF and should not be given in patients with second- or third-degree heart block or bradycardia
Phentolamine (2 min, 15–30 min)	IVB dose 5 mg; additional bolus doses every 10 min as needed	Used in hypertensive emergencies induced by catecholamine excess (pheochromocytoma, monamine oxidase inhibitors interactions with food and/or drugs, cocaine toxicity, amphetamine overdose, or clonidine withdrawal)

CI = contraindication; ICP = intracranial pressure.

Table 23. Agents Preferred for Hypertensive Crises According to Comorbidities

Comorbidity	Preferred Agents	Comments
Acute aortic dissection	Labetalol, esmolol	Requires rapid lowering of SBP to ≤ 120 mm Hg within 20 min; β-blocker should be given before vasodilator (nicardipine or NTP) if needed for BP control or to prevent reflex tachycardia or inotropic effect; SBP ≤ 120 mm Hg should be achieved within 20 min
Acute coronary syndromes	Esmolol or NTG (preferred), labetalol, nicardipine	Nitrates given in the presence of PDE-5 inhibitors may induce profound hypotension; contraindications to β-blockers include moderate to severe LV failure with pulmonary edema, right ventricular infarction, bradycardia (< 60 beats/min), hypotension (SBP < 100 mm Hg), poor peripheral perfusion, second- or third-degree heart block, and reactive airway disease
Acute pulmonary edema	Clevidipine, NTG, NTP	β-Blockers contraindicated; NTG preferred for ADHF
Acute renal failure	Clevidipine, fenoldopam, nicardipine	
Eclampsia or preeclampsia	Labetalol, nicardipine, hydralazine (second line)	Requires rapid BP lowering to < 140 mm Hg within first hour; ACE inhibitor, ARBs, renin inhibitors, and NTP contraindicated
Perioperative HTN (BP ≥ 160/90 mm Hg or SBP elevation > 20% of the preoperative value that persists > 15 min)	Clevidipine, esmolol, nicardipine, NTG	Intraoperative HTN is most common during anesthesia induction and airway manipulation
Acute sympathetic discharge or catecholamine excess states (e.g., pheochromocytoma, post-carotid endarterectomy status)	Clevidipine, nicardipine, phentolamine (Note: Avoid unopposed β-blockade)	Requires rapid lowering of BP
Acute intracranial hemorrhage	IV continuous infusion	Lower BP in those who present with SBP > 220 mm Hg with continuous IV infusion and close BP monitoring; immediate lowering of SBP < 140 mm Hg is not of benefit and may be harmful. Avoiding medications that can increase ICP and worsen cerebral ischemia (hydralazine, NTG, and NTP)
Acute ischemic stroke	No preference of agent	Early initiation or resumption of antihypertensive treatment indicated only in (1) patients treated with tissue-type plasminogen activator to an SBP < 185/110 mm Hg and (2) patients with SBP > 220 mm Hg or DBP > 120 mm Hg; cerebral autoregulation in the ischemic penumbra of the stroke is grossly abnormal and rapid reduction of BP can be harmful; reinitiate antihypertensive therapies in those with preexisting HTN after neurologic stability

ARB = angiotensin receptor blocker; NTP = nitroprusside.

Patient Cases

11. A 68-year-old man with a history of stage 5 chronic kidney disease receiving hemodialysis, hypertension, CAD post-MI, moderately depressed LVEF, and gastroesophageal reflux disease presents with acute-onset shortness of breath and chest pain. After his recent dialysis, he was nonadherent to medical therapy for 2 days and noticed he had gained 2 kg in 24 hours. His baseline orthopnea worsened to sleeping sitting up in a chair for the 2 nights before admission. He admits smoking cocaine within the past 24 hours and developed acute-onset chest tightness with diaphoresis and nausea, and his pain was 7/10. He went to the ED, where his blood pressure was 250/120 mm Hg. He had crackles halfway up his lungs on examination, and chest radiography detected bilateral fluffy infiltrates with prominent vessel cephalization. His ECG revealed sinus tachycardia, heart rate 122 beats/minute, and ST-segment depressions in leads 2, 3, and aVF. He was admitted for a hypertensive emergency. Laboratory results are as follows: BUN 48 mg/dL, SCr 11.4 mg/dL, BNP 2350 pg/mL, troponin T 1.5 ng/L (less than 0.1 mcg/L), creatine kinase 227 units/L, and creatine kinase-MB 22 units/L. Which medication is best for this patient's hypertensive emergency?

    A. Intravenous nitroglycerin 5 mcg/minute titrated to a 25% reduction in MAP.

    B. Labetalol 2 mcg/minute titrated to a 50% reduction in MAP.

    C. Sodium nitroprusside 0.25 mcg/kg/minute titrated to a 25% reduction in MAP.

    D. Clonidine 0.1 mg orally every 2 hours as needed for a 50% reduction in MAP.

12. A 56-year-old white woman with a long history of hypertension because of nonadherence and recently diagnosed HF (EF 35%) presents to the local ED with blood pressure 210/120 mm Hg and heart rate 105 beats/minute. She states that she felt a little lightheaded but that she now feels okay. She ran out of her blood pressure medications (including hydrochlorothiazide, carvedilol, and lisinopril) 3 days ago. Her current laboratory values are within normal limits. Which medication is best for this patient?

    A. Sodium nitroprusside 0.25 mcg/kg/minute titrated to a 25% reduction in MAP.

    B. Labetalol 80 mg intravenously; repeat until blood pressure is less than 120/80 mm Hg.

    C. Resumption of home medications; refer for follow-up within 2 days.

    D. Resumption of home medications; initiate amlodipine 10 mg daily; refer for follow-up in 1 week.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

This patient's atypical symptoms, ST-segment depression on ECG, and positive biomarkers for myocardial necrosis suggest NSTE-ACS. She has at least three risk factors for CAD, a history of CAD (prior MI), and positive troponins, which place her at high risk of future events. In such high-risk patients, an early invasive strategy (as in Answers A and B) is used to determine whether occluded or partly occluded arteries exist, which ones can be intervened on, and whether to make an intervention. An ischemia-guided approach, also called "medical management," as in Answers C and D, would not be preferred because of this patient's risk category (i.e., positive troponins). Dual antiplatelet therapy (aspirin plus a $P2Y_{12}$ inhibitor) is indicated for an early invasive strategy in managing an NSTE-ACS. In patients undergoing PCI, clopidogrel, prasugrel, or ticagrelor is appropriate (Answer A is correct). After an initial bolus of 60 units/kg and an infusion of 12 units/kg/hour (Answer A is correct; Answer D is incorrect), UFH can be titrated to an aPTT of 50–70 seconds. Aspirin alone without a $P2Y_{12}$ agent, as in Answer B, would not provide adequate antiplatelet therapy. Furthermore, enoxaparin would need to be dosed with a 30-mg intravenous bolus before initiating twice-daily subcutaneous dosing because this patient has positive troponins. Glycoprotein IIb/IIIa inhibitors, as in Answer C, can be useful in high-risk patients, typically those with positive troponins; however, their benefit has been shown mainly when UFH, not low-molecular-weight heparin, is given as the anticoagulant.

2. Answer: C

Of importance, this patient case occurs in the context of elective stent placement, not after ACS. In the non-ACS setting, the duration of DAPT is determined by the type of stent placed (bare metal stent vs. drug-eluting stent). After elective drug-eluting stent placement, DAPT is recommended for at least 6 months because the risk of in-stent thrombosis is highest during this time (Answer C is correct). The recommendation is for at least 1 month after bare metal stent placement because endothelialization of the stent usually occurs early, typically within 1 month after stenting (Answer A is incorrect). Bleeding risk may be a reason to consider earlier termination (after at least 1 month) of DAPT after bare metal stent placement. Although European guidelines consider 3 months of DAPT after drug-eluting stent placement appropriate, the recommended minimum according to the U.S. guidelines is 6 months (Answer B is incorrect). Twelve months of therapy is recommended after ACS (Answer D is incorrect).

3. Answer: D

Because the patient presents to a hospital that can do a primary PCI with stent implantation, this is the preferred reperfusion strategy (Answers B and C are incorrect). Answer A is incorrect because an anticoagulant agent must be administered in addition to antiplatelet therapy. Reperfusion with fibrinolytic therapy (Answers B and C) would only be considered if PCI were expected to be delayed by more than 120 minutes. In addition, Answer C is incorrect because bivalirudin has not been studied with lytic therapy. Answer D – reperfusion with primary PCI, DAPT with aspirin and prasugrel, and dosing of bivalirudin as an anticoagulant strategy – is correct.

4. Answer: C

Unlike the patient in case 3, this patient presents with a STEMI to a rural community hospital where the nearest hospital with catheterization laboratory facilities is more than 120 minutes away (i.e., lytics are indicated). He presents within the window for fibrinolytic therapy consideration (less than 6 hours after chest pain onset) and has no obvious contraindications. Because he is still having ischemic chest pain and ST-segment elevation, he should benefit from reperfusion therapy. He is experiencing complete heart block and bradycardia, which could indicate an occlusion above the area perfusing his sinoatrial or atrioventricular nodes. Enoxaparin is a treatment option for anticoagulant therapy given in conjunction with fibrinolytics, but the patient is at higher risk of bleeding from impaired enoxaparin clearance and needs a dosage adjustment. Furthermore, he is older than 75, beyond the age at which the intravenous bolus should be given, and the alteplase dosing is incomplete (Answer A is incorrect). Simply treating this patient conservatively with UFH alone in the setting of ongoing chest pain, shortness of breath, and pulmonary edema is not optimal (Answer B is incorrect). Diagnostic catheterization and possible PCI to determine whether an artery can be reperfused may be desirable but is complicated because the patient's SCr is elevated (2.5 mg/dL), and he is in a rural

hospital, where he cannot be assessed quickly enough (within 90–120 minutes) (Answer D is incorrect). Because of the shorter half-life and ease of administration of tenecteplase, tenecteplase may be preferable to alteplase. Clearance of UFH with tenecteplase is not as altered as with enoxaparin, and it would be a more appropriate therapy than enoxaparin in combination with a thrombolytic (Answer C is correct).

5. Answer: C

This patient, who has ADHF, is receiving a β-blocker. Although long-term β-blockers can improve HF symptoms and reduce mortality, they can also worsen symptoms in the short term. It is recommended to keep the maintenance β-blocker therapy at the same or at a slightly lower dose compared with the outpatient therapy in patients with ADHF; increasing the β-blocker dose before reaching euvolemia might acutely worsen his clinical picture (Answer A is incorrect). In patients admitted with volume overload without substantial signs of reduced CO, it is reasonable to try intravenous loop diuretics initially (Answer C is correct). As gut edema increases, oral loop diuretics (notably furosemide) become less effective because of decreased absorption. Sodium nitroprusside could be useful if signs and symptoms of hypoperfusion were present. Because this patient presents mainly with warm and wet symptoms, diuretics would be first-line (Answer B is incorrect). Milrinone is an inotropic drug. Because of their adverse effects, inotropes are recommended in cold and wet exacerbations only after vasodilatory medications have failed (Answer D is incorrect).

6. Answer: A

Intravenous vasodilators such as nitroglycerin (Answer A) and sodium nitroprusside (Answer B) are reasonable if intravenous diuretics fail and the patient progresses to acute pulmonary edema. Both agents rapidly cause venous vasodilation and reduce pulmonary filling pressures, which can relieve acute shortness of breath. Answer A, nitroglycerin, is optimal for this patient, given his declining renal function and the concern for increased risk of thiocyanate toxicity with sodium nitroprusside in this setting (Answer B is incorrect). Dobutamine is typically used in states of low CO decompensation and is counteracted by concomitant β-blocker therapy, making it a poor choice in patients receiving β-blockers (Answer C is incorrect). Although milrinone is a more acceptable inotropic agent in a patient receiving β-blockers, the dosing strategy is inappropriate as an initial dose (Answer D is incorrect). Finally, inotropes are generally reserved for patients when other therapies have failed.

7. Answer: A

Signs of a decreased CO state in HF (e.g., increased SCr, decreased mental status, cool extremities) suggest a cold and wet state, and adjunctive therapy is indicated. Positive inotropic agents such as milrinone will increase CO to maintain perfusion to vital organs. Milrinone will also vasodilate the peripheral vessels to unload the heart (lower SVR). Although dobutamine would be a potential choice in this patient, it is not recommended in patients receiving β-blockers, and the initial starting dose is too aggressive (Answer B is incorrect). Although this patient has low blood pressure, his elevated SVR suggests that he will tolerate the vasodilatory effects of milrinone as long as it is appropriately renally adjusted for worsening renal dysfunction (Answer A is correct). Nitroprusside would be relatively contraindicated in patients with an SBP less than 100 mm Hg and is absolutely contraindicated in patients with an SBP less than 90 mm Hg (Answer C is incorrect). Phenylephrine has no positive beta effects; therefore, it will not augment contractility. In addition, it will cause vasoconstriction through alpha stimulation, which will further increase SVR and probably worsen CO (Answer D is incorrect). Vasoconstrictors are reserved for patients in cardiogenic shock.

8. Answer: A

Treatment options for sustained VT depend on concomitant disease states, particularly LVEF (40% cutoff). In a patient with LV dysfunction, class I agents such as procainamide are contraindicated (Answer D is incorrect). In a patient whose CrCl is less than 60 mL/minute, sotalol requires a considerable dose reduction to avoid an excess risk of torsades de pointes. Sotalol is not an effective cardioversion drug but is more useful for preventing future episodes of arrhythmias (maintaining sinus rhythm) once sinus rhythm is achieved (Answer B is incorrect). Dofetilide is indicated only for AF, not for ventricular arrhythmias; similarly, cardioversion rates with dofetilide are low (Answer C is incorrect). Amiodarone is first-line therapy for sustained VT in patients with severe renal insufficiency, HF, and SHD (Answer A is correct).

9. Answer: C

With the prolonged half-life of amiodarone and extensive fat tissue volume of distribution, hyperthyroid adverse effects would be expected to last for 3–5 half-lives of the drug, which is 5–8 months (Answer C is correct; Answer A is incorrect). Although therapeutic concentrations may decrease substantially by then, 1 month is too soon for the effects to subside (Answer B is incorrect). Although some iodine and amiodarone molecules will probably remain absorbed in fat stores for years, if not for life, therapeutic concentrations should not exist for longer than what is predicted by the half-life (Answer D is incorrect).

10. Answer: D

This patient is having QT prolongation with sotalol, placing her at an elevated risk of developing life-threatening torsades de pointes. Sotalol should be discontinued immediately (Answers A and B are incorrect). Given the QT prolongation that occurred with sotalol, the same will probably occur with dofetilide (Answer C is incorrect). Amiodarone is associated with minimal risk of torsades de pointes and therefore would be an appropriate alternative agent to prevent ventricular arrhythmias (Answer D is correct).

11. Answer: A

Hypertensive emergency should be treated immediately by no more than a 25% reduction in MAP over the first hour, followed by a further reduction to a blood pressure of 160/100 mm Hg over the next 2–6 hours. The patient's comorbidities guide the optimal therapy. His dialysis and SCr of 11.4 mg/dL are contraindications to sodium nitroprusside (Answer C is incorrect) because of possible thiocyanate toxicity. Labetalol (and β-blockers in general) is controversial in patients who have taken cocaine, but its nonselective nature makes it an option; however, a reduction of 50% initially is too rapid a decrease in blood pressure for safety (Answer B is incorrect). Clonidine is not appropriate for a hypertensive emergency because its oral form is difficult to titrate and can lead to precipitous drops in blood pressure beyond the goal 25% reduction and possibly stroke or worsening MI (Answer D is incorrect). Nitroglycerin is optimal, considering the patient's lack of contraindications to this therapy and his evolving MI and symptoms of HF (Answer A is correct).

12. Answer: C

In an asymptomatic hypertensive crisis (without acute target-organ damage), giving intravenous medications, as in Answers A and B, and admitting the patient to the hospital are unnecessary (Answers A and B are incorrect). This patient is likely presenting because of recent nonadherence. Resuming her home medications (Answer C is correct) at this time would be most appropriate, with a close follow-up to ensure that her prescribed regimen is working. Adding a fourth agent (Answer D is incorrect) at this time is unnecessary, considering that her disease could be controlled on her current drug regimen if she were adherent. Follow-up should occur within the first few days, rather than waiting 1 week.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

This patient's chest pain, ST-segment depression on ECG, and positive biomarkers for myocardial necrosis suggest NSTE-ACS. Because of his presentation characteristics, he is at a high enough risk to warrant cardiac catheterization (invasive strategy). This invasive strategy is used to determine whether occluded or partly occluded epicardial arteries exist, which ones can be intervened on, and whether to do PCI (percutaneous transluminal coronary angioplasty with or without stenting). Initial therapy for ACS usually consists of morphine, oxygen, nitroglycerin, and aspirin, but only aspirin has been shown to reduce mortality from these initial treatments. Aspirin should be given as soon as possible after hospital presentation and continued indefinitely, if tolerated. According to clinical trials, guidelines, and experience, an initial dose of 162–325 mg is recommended (Answers B and D are not the best choices of dosing for an acute episode). Aspirin, together with a $P2Y_{12}$ receptor antagonist, is indicated for an early invasive strategy in the management of UA/NSTEMI, improving outcomes. The 2014 NSTE-ACS guidelines give a class I recommendation for clopidogrel, ticagrelor, and prasugrel in ACS for patients undergoing PCI. The choice of which $P2Y_{12}$ receptor antagonist to use in the ACS setting depends on patient presentation, contraindications, and whether PCI is involved; in this case, any of the three $P2Y_{12}$ antagonists would be appropriate. The anticoagulation strategy treatment for ACS generally includes one anticoagulant (UFH, low-molecular-weight heparin, fondaparinux, or bivalirudin). When UFH is chosen as an anticoagulant strategy, the dose used for ACS is a 60-unit/kg bolus and a 12-unit/kg/hour infusion (Answer A is incorrect). Regarding dosing, bivalirudin (Answer D) would be an appropriate anticoagulation strategy; however, the initial aspirin dose should be higher, and a nitroglycerin drip would not be the best choice, given his right-sided MI (low blood pressure, low heart rate). Answer A is reasonable in patients without contraindications when hypertension or ongoing ischemia is a concern; however, initiating oral therapy within 24 hours is preferred in most patients as long as they have no signs of HF, evidence of low output state, increased risk of cardiogenic shock, or other contraindications to β-blockade. β-Blockers should initially be avoided in this patient, given his blood pressure and decreased baseline heart rate. An intravenous ACE inhibitor (Answer B) should not be given to patients within the first 24 hours of ACS because of the increased risk of hypotension. Answer C includes DAPT and an appropriate anticoagulant dose (Answer C is correct).

2. Answer: A

The NSTE-ACS guidelines recommend the use of one anticoagulant during an acute event. Enoxaparin, UFH, and bivalirudin are all recommended as class I agents for the invasive management of NSTE-ACS. However, fondaparinux (Answer C) is not optimal because of the increased risk of catheter-related thrombosis associated with its use in the catheterization laboratory. The NSTE-ACS guidelines advise the use of an additional anticoagulant with class IIa activity (heparin or bivalirudin) if fondaparinux was an initial anticoagulant when the patient underwent intervention, whereas the PCI guidelines give fondaparinux a class III or harmful recommendation. Of the remaining three options, UFH (Answer A) is preferred because of its dosage and rapid clearance regardless of renal function. The UFH bolus should be limited to 4000 units, and the initial infusion should be limited to 1000 units/hour. Both enoxaparin (Answer B) and bivalirudin (Answer D) would be appropriate but would need to be dose adjusted, given this patient's CrCl of less than 30 mL/minute. However, the doses in Answers B and D would be appropriate for patients with a normal CrCl.

3. Answer: B

An anticoagulant is required for PCI. Options include UFH, bivalirudin, and enoxaparin. Because this patient had a significantly low Plt with his most recent heparin exposure and was confirmed to have HIT, using any of the GP IIb/IIIa inhibitors (Answers A and C) would be unwise for ACS treatment because these agents are usually combined with UFH. Furthermore, GP IIb/IIIa inhibitors are antiplatelets, and the patient will still need an additional agent with anticoagulant activity. Thrombolytic therapy is not recommended for NSTE-ACS and would be inappropriate in this patient (Answer D is incorrect). Answer D is also incorrect because enoxaparin carries a 10% risk of cross-reactivity if HIT is suspected. Bivalirudin (Answer B), a direct thrombin inhibitor, would be the treatment of choice in patients with HIT undergoing PCI.

4. Answer: D

β-Blocker therapy can cause HF decompensation, particularly when the β-blocker is titrated too quickly or initiated in patients who are not euvolemic. Although administering β-blockers within the first 24 hours is beneficial in STEMI, this patient has several risk factors that would be considered contraindications to initial β-blockade. This patient's clinical condition suggests he is not euvolemic, and aggressive diuresis should be tried before a β-blocker is initiated for him. In addition, intravenous β-blocker therapy (Answer B) would place him at an even greater risk of cardiogenic shock. Answers A and C are inappropriate because the doses are fairly aggressive for a patient with an EF of 25% and marginal blood pressure. Answer D is correct; however, before discharge, this patient should be reevaluated for the initiation of low-dose β-blocker therapy.

5. Answer: B

Dual antiplatelet therapy is recommended for at least 12 months in patients presenting with ACS. Early discontinuation of DAPT is reasonable when the risk of morbidity exceeds the expected benefit (class IIa), as in the case of bleeding. Answers C and D do not represent the minimum time interval, given that the patient has no known risk of bleeding. Prasugrel (Answer B) would be preferable to clopidogrel (Answer A) in this scenario because it would be faster in onset; clopidogrel would take about 6 hours for maximal platelet inhibition after a 300-mg LD. Subgroup analysis of a randomized placebo-controlled trial comparing the effectiveness of prasugrel and clopidogrel showed the superiority of prasugrel, especially for patients presenting with a STEMI (Answer B is correct).

6. Answer: C

This patient is well perfused and can be classified in Forrester hemodynamic subset II (warm and wet). Because the patient has pulmonary congestion (shortness of breath, dyspnea at rest), intravenous diuretics are first-line therapy. Nitroglycerin (Answer C) is best in this setting because vasodilatory agents can be used in conjunction with intravenous diuretics to improve acute pulmonary edema. When adjunctive therapy is needed in addition to loop diuretics, intravenous vasodilators should be considered over inotropic agents when blood pressure is adequate. Dobutamine (Answer A) and milrinone (Answer B) primarily increase CO, which is not a problem in warm and wet exacerbations. In addition, the adverse effects of these agents (increased mortality, proarrhythmia) limit their use. Intravenous metoprolol (Answer D) should be used extremely cautiously because of its negative inotropic effects and because this patient is not in a euvolemic state.

7. Answer: D

This patient has a depressed LVEF less than 40%; therefore, her AAD therapy options are limited. Procainamide (Answer A) is indicated only in secondary prevention of sustained VT in patients with a normal LVEF greater than 40%; if given to this patient, it could worsen her HF. Metoprolol (Answer B) is indicated for treating patients with asymptomatic nonsustained VT and SVT associated with CAD. This patient had an episode of sustained VT; therefore, therapy beyond β-blockade is warranted. Her QTc interval is not prolonged at 380 milliseconds, and her serum magnesium concentration is within normal limits; thus, she does not need intravenous magnesium therapy (Answer C). Amiodarone (Answer D) is first line for patients without contraindications because of its efficacy and safety in patients with an LVEF less than 40%.

8. Answer: B

This patient has target-organ damage from poorly controlled hypertension in the form of retinal hemorrhaging. Fenoldopam is contraindicated for treating hypertensive emergencies in the setting of glaucoma (Answer A is incorrect). Nicardipine is appropriate for this patient, given the details of this case (Answer B is correct). Although labetalol is effective for treating hypertensive emergency, this patient has a history of asthma and a low heart rate, making labetalol a less-than-ideal option for treating her symptoms (Answer C is incorrect). The antihypertensive effects of enalaprilat depend on a patient's renin activity, which is unknown in this case. Therefore, the blood pressure–reducing effects may be more difficult to control than when using a drug having a more consistent effect in individuals. In addition, the bolus nature of the drug is not ideal for tightly controlling blood pressure with no more than a 25% reduction in MAP. Continuous infusion drugs are preferable for easier titration to effect in a hypertensive emergency (Answer D is incorrect).

9. Answer: C

The Cardiac Arrest Study Hamburg trial compared ICD with AAD in survivors of cardiac arrest for secondary prevention of SCD. The propafenone (Answer A) study

arm was discontinued early because of its significantly (61%) higher mortality rate compared with the ICD arm (Answer A is incorrect). Although this trial had a small sample size that prevented a statistically significant difference in total mortality in ICD-treated patients versus patients treated with either amiodarone or metoprolol, the incidence of sudden death was significantly lower in patients with an ICD (Answer C is correct; 33% vs. 13%; p=0.005). The Antiarrhythmics Versus Implantable Defibrillators trial also evaluated ICD implantation versus AAD therapy (primarily amiodarone) in survivors of SCD. Patients with ICDs had a significantly higher rate of survival than did those treated with drug therapy (89% vs. 82%; p<0.02), making Answer C preferable to all the other options (Answers B and D are incorrect).

10. Answer: C

The number needed to treat can be calculated as 1/absolute risk reduction. Because the absolute risk reduction in mortality at 60 months was 7.2% with ICD versus placebo, 1/0.072 would be used to calculate the number of patients needed to treat to prevent one death during this time. About 14 patients (Answer C) would need to be treated with ICD to prevent one death in 60 months versus placebo. Other calculations in this fashion, including relative risk reduction and 100% minus the absolute or relative risk reduction, provide no useful information for interpreting the trial results and yield an incorrect number of patients (Answers A, B, and D are incorrect).

11. Answer: D

International Pharmaceutical Abstracts (Answer A) is a database of primarily pharmaceutical abstracts in more than 750 journals, including foreign and state pharmacy journals, in addition to key U.S. medical and pharmacy journals. Many of the citations are not included on Medline, so a broader search can be done; however, subject descriptors are not consistently defined in a uniform way, and multiword terms are often cited backward. The Iowa Drug Information Service database (Answer B) offers full-text articles from 1966 to the present in about 200 medical and pharmacy journals (based primarily in the United States). This database is updated monthly, and newly available articles may take longer to access from this service. The Clin-Alert database (Answer C) contains more than 100 medical and pharmacy journals focused on adverse events, drug interactions, and medical-legal issues. This database is used primarily to look up adverse events (especially recent reports) associated with medications. Excerpta Medica (Answer D) is a comprehensive database of more than 7000 journals from 74 countries dating from 1974 to the present. Recently published articles appear in the system within 10 days of article publication, and it often contains data not found in a typical Medline search.

12. Answer: B

MedWatch is a post-FDA approval program established by the FDA for health care professionals to report the adverse events that occur after a drug is approved. Although MedWatch is commonly used only for reporting serious reactions to the FDA and would not be mandatory in this case (Answer A is incorrect), it can be used to report any adverse event. Information recorded on these forms is reported to the manufacturer and used to determine whether black box warnings are necessary or whether new adverse effects occur with a drug. The Joint Commission requires that all institutions have a definition of an ADR that can be understood and remembered by all health care professionals at the institution (Answer B is correct). In addition, The Joint Commission requires that each drug dose administered be monitored for adverse effects, that each institution have a system in place for reporting ADRs, and that the institution ensure that the reporting mechanism identifies all key ADRs. The Naranjo algorithm is used to determine the likelihood of cause and effect from a presumed drug-induced event but is not required (Answer C is incorrect). Answer D is incorrect because serious adverse effects are reportable to the FDA, as are severe and life-threatening events.

13. Answer: B

Because the pharmacy and therapeutics committee wants to discover whether the new drug is worth the extra cost for the added mortality benefits it can provide for patients with decompensated HF compared with available therapies, a cost-effectiveness analysis (Answer B is correct) is the best pharmacoeconomic analysis. Cost-minimization analysis (Answer A is incorrect) determines whether a therapeutically equivalent drug within a class that provides the same therapeutic outcome as other available drugs can be used for less cost. Cost-utility analysis (Answer D is incorrect) determines whether a drug can improve the quality of a patient's life more than other available therapies. Cost-benefit analysis (Answer C is incorrect) evaluates new programs or services to determine whether they provide enough benefit to justify their cost.

Infectious Diseases I

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Learning Objectives

1. Identify the presenting signs and symptoms, etiology, and risk factors of respiratory tract infections, urinary tract infections, skin and soft tissue infections, osteomyelitis, central nervous system (CNS) infections, intra-abdominal infections, *Clostridioides difficile* infections, and endocarditis.
2. Recommend appropriate treatment for patients with respiratory tract infections, urinary tract infections, skin and soft tissue infections, osteomyelitis, CNS infections, intra-abdominal infections, *C. difficile* infections, and endocarditis.
3. Select appropriate preventive therapy for CNS infections, endocarditis, and surgical wound infections.

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. P.E. is a 56-year-old man who comes to the clinic with a 3-day history of fever, chills, pleuritic chest pain, malaise, and productive cough. In the clinic, his temperature is 102.1°F (38.9°C) (all other vital signs are normal). His chest radiograph reveals consolidation in the right lower lobe. His white blood cell count (WBC) is 14,400 cells/mm^3, but all other laboratory values are normal. He is given a diagnosis of community-acquired pneumonia (CAP). He has not received any antibiotics in 5 years and has no chronic disease states. Which is the best empiric therapy for P.E.?
   A. Doxycycline 100 mg orally twice daily.
   B. Cefuroxime axetil 250 mg orally twice daily.
   C. Levofloxacin 750 mg orally daily.
   D. Trimethoprim/sulfamethoxazole double strength orally twice daily.

2. H.W. is a 38-year-old woman who presents with a fever, malaise, dry cough, nasal congestion, and severe headaches. Her symptoms began suddenly 3 days ago, and she has been in bed since then. She reports no other illness in her family, but several people have recently called in sick at work. It is influenza season. Which is best for H.W.?
   A. Azithromycin 500 mg, followed by 250 mg daily orally for 4 more days.
   B. Amoxicillin/clavulanic acid 875 mg orally twice daily for 5 days.
   C. Oseltamivir 75 mg twice daily orally for 5 days.
   D. Symptomatic treatment only.

3. A study is designed to assess the risk of pneumococcal pneumonia in older adults 10 years or more after receiving their last pneumococcal vaccination, compared with older adults who have never received any pneumococcal vaccinations. Which study design is best?
   A. Case series.
   B. Case-control study.
   C. Prospective cohort study.
   D. Randomized controlled trial.

4. A.B. is a 63-year-old woman who presents to the emergency department with left leg pain and erythema. The pain and erythema have worsened over the past 24 hours, and in the emergency department, large blisters formed and the leg became numb. The left leg is significantly swollen with a large area of erythema and large bullae extending from the thigh to the upper leg. There is crepitus within the soft tissue. A.B. is found to have rapidly progressing necrotizing fasciitis. A.B. has normal renal function and no known drug allergies. Which is the best empiric therapy for A.B.?
   A. Vancomycin 15 mg/kg intravenously every 12 hours.
   B. Piperacillin/tazobactam 4.5 g intravenously every 8 hours.
   C. Vancomycin 15 mg/kg intravenously every 12 hours plus meropenem 1 g intravenously every 8 hours plus clindamycin 900 mg intravenously every 8 hours.
   D. Linezolid 600 mg intravenously every 12 hours plus ceftriaxone 1 g intravenously every 24 hours plus azithromycin 500 mg intravenously daily.

5. N.R. is a 28-year-old woman who presents to the clinic with a 2-day history of dysuria, frequency, and urgency. She has no significant medical history, and the only drug she takes is oral contraceptives. Which is the best empiric therapy for N.R.?
   A. Nitrofurantoin extended release (ER) 100 mg orally twice daily for 3 days.
   B. Ciprofloxacin 500 mg orally twice daily for 7 days.
   C. Trimethoprim/sulfamethoxazole double strength orally twice daily for 3 days.
   D. Cephalexin 500 mg orally four times daily for 3 days.

6. B.Y. is an 85-year-old woman who is bedridden and lives in a nursing home. She is chronically catheterized, and her urinary catheter was last changed 3 weeks ago. Today, her urine is cloudy, and a urinalysis reveals many bacteria. B.Y. is not noticing any symptoms. A urine culture is obtained. Which option is best for B.Y.?
   A. No therapy because she is chronically catheterized and has no symptoms.
   B. No antibiotic therapy, but the catheter should be changed.
   C. Ciprofloxacin 500 mg orally twice daily for 7 days and a new catheter.
   D. Ciprofloxacin 500 mg orally twice daily for 14–21 days without a change in catheter.

7. V.E. is a 44-year-old man who presents to the emergency department with a warm, erythematous, and painful right lower extremity. There is no raised border at the edge of the infection. Three days ago, he scratched his leg on a barbed wire fence on his property (no puncture wound associated with the fence). His temperature has been as high as 101.8°F (38°C) with chills. Doppler studies of his lower extremity are negative. Blood cultures are negative. Which is the best empiric therapy for V.E.?
   A. Cefazolin 1 g intravenously every 8 hours.
   B. Penicillin G 2 million units intravenously every 4 hours.
   C. Piperacillin/tazobactam 3.375 g intravenously every 6 hours.
   D. Enoxaparin 80 mg subcutaneously twice daily and warfarin 5 mg daily orally.

8. R.K. is a 36-year-old woman who presents to the emergency department with a severe headache and neck stiffness. Her temperature is 99.5°F (37.5°C). After a negative computed tomographic scan of the head, a lumbar puncture reveals the following: glucose 54 mg/dL (peripheral, 104 mg/dL), protein 88 mg/dL, and WBC 220 cells/mm^3 (100% lymphocytes). The Gram stain reveals no organisms. Which option describes the best therapy for R.K.?
   A. This is aseptic (probably viral) meningitis, and no antibiotics are necessary.
   B. Administer ceftriaxone 2 g intravenously every 12 hours until the cerebrospinal fluid (CSF) cultures are negative for bacteria.
   C. Administer ceftriaxone 2 g intravenously every 12 hours and vancomycin 15 mg/kg intravenously every 12 hours until the CSF cultures are negative for bacteria.
   D. Administer acyclovir 500 mg intravenously every 8 hours until the CSF culture results are complete.

9. L.G. is a 49-year-old woman with a history of mitral valve prolapse. She presents to her physician's office with malaise and a low-grade fever. Her physician notes that her murmur is louder than usual and orders blood cultures and an echocardiogram. A large vegetation is observed on L.G.'s mitral valve, and her blood cultures are growing *Enterococcus faecalis* (susceptible to all antibiotics). Which is the best therapy for L.G.?
   A. Penicillin G plus gentamicin for 2 weeks.
   B. Vancomycin plus ceftriaxone for 2 weeks.
   C. Ampicillin plus ceftriaxone for 4–6 weeks.
   D. Cefazolin plus gentamicin for 4–6 weeks.

10. N.L. is a 28-year-old woman with no significant medical history. She reports to the emergency department with fever and severe right lower quadrant pain. The pain had been dull for the past few days, but it suddenly became severe during the past 8 hours. Her temperature is 103.5°F (39.7°C), and she has rebound tenderness on abdominal examination. She is taken to surgery immediately,

where a perforated appendix is diagnosed and repaired. Which is the best follow-up antibiotic regimen?

A. Vancomycin 1000 mg intravenously every 12 hours plus metronidazole 500 mg intravenously every 8 hours.
B. Cefazolin 1 g intravenously every 8 hours plus ciprofloxacin 400 mg intravenously every 12 hours.
C. Ceftriaxone 1 g intravenously every 24 hours plus metronidazole 500 mg intravenously every 8 hours.
D. No antibiotics needed after surgical repair of a perforated appendix.

11. O.R. is a 73-year-old man who presents to the emergency department with a 3-day history of fever, chills, frequency, urgency, and perineal pain. A urinalysis reveals many bacteria. A rectal examination reveals a swollen, tender prostate. He is given a diagnosis of acute bacterial prostatitis. Which is the best regimen for this patient?

A. Amoxicillin/clavulanate 875 orally twice daily for 7 days.
B. Trimethoprim/sulfamethoxazole double strength orally twice daily for 14 days.
C. Cefprozil 500 mg orally twice daily for 21 days.
D. Ciprofloxacin 500 mg orally twice daily for 28 days.

12. J.M. is a 72-year-old woman with a history of atrial fibrillation, hypertension, a right total hip replacement 8 months earlier, and Crohn disease. She has no drug allergies. She presents to the hospital with increasing pain in her prosthetic hip over the past month. There is concern about hip osteomyelitis. Bone cultures are growing methicillin-sensitive *Staphylococcus aureus*. J.M. has normal renal function and no known drug allergies. Which is the best antibiotic regimen for this patient with a prosthetic hip infection?

A. Vancomycin 1000 mg intravenously every 12 hours plus rifampin 300 mg orally twice daily for 2 weeks.
B. Cefazolin 2 g intravenously every 8 hours plus rifampin 300 mg orally twice daily for 6 weeks followed by long-term oral antibiotics.
C. Nafcillin 1 g intravenously every 4 hours for 6 weeks.
D. Daptomycin 6 mg/kg intravenously daily for 6 weeks followed by long-term oral antibiotics.

13. B.K. is a 58-year-old woman (height 66 inches, weight 82 kg) who is scheduled to undergo a total knee replacement tomorrow. She has no significant medical history and no drug allergies. Which is the best surgical prophylaxis regimen for this patient?

A. Cefazolin 2 g within 1 hour of the incision and no doses postoperatively.
B. Cefazolin 2 g within 4 hours of the incision and three doses every 8 hours postoperatively.
C. Cefazolin 1 g within 1 hour of the incision and three doses every 8 hours postoperatively.
D. Cefazolin 1 g within 4 hours of the incision and no doses postoperatively.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-Centered Pharmacotherapy
    a. Task 1: Knowledge statements: 1–7, 10–13, 15; Task 4: Knowledge statements: 2–6

I. RESPIRATORY TRACT INFECTIONS

A. Pneumonia
   1. Pneumonia is the most common cause of death attributable to infectious diseases (very high mortality rate in older adults) and in the top 10 causes of death in the United States.
   2. Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection (0.6%–1.1% of all hospitalized patients). There is a higher incidence in patients in the intensive care unit recovering from thoracic or upper abdominal surgery and in older adults.
   3. Mortality rates
      a. Community-acquired pneumonia (CAP) without hospitalization: Less than 1%
      b. CAP with hospitalization: About 14%
      c. Ventilator-associated pneumonia (VAP): About 20%–50%

B. Community-Acquired Pneumonia
   1. Definition: Acute infection of the pulmonary parenchyma, accompanied by an acute infiltrate consistent with pneumonia on chest radiograph or auscultatory findings, acquired in the community.
   2. Symptoms of CAP are listed below. Older adults often have fewer and less severe findings (mental status changes are common).
      a. Fever or hypothermia
      b. Rigors
      c. Sweats
      d. New cough with or without sputum (90%)
      e. Chest discomfort (50%)
      f. Onset of dyspnea (66%)
      g. Fatigue
      h. Myalgias
      i. Abdominal pain
      j. Anorexia
      k. Headache
   3. Predictors of a complicated course of CAP are listed below. Hospitalization should be based on the severity-of-illness scores (e.g., CURB-65, pneumonia severity index).
      a. Age older than 65 years
      b. Comorbid illness (diabetes mellitus, congestive heart failure, lung disease, renal failure, liver disease)
      c. High temperature: more than 101°F (38°C)
      d. Bacteremia
      e. Altered mental status
      f. Immunosuppression (e.g., steroid use, cancer)
      g. High-risk etiology (*Staphylococcus aureus, Legionella,* gram-negative bacilli, anaerobic aspiration)
      h. Multilobe involvement or pleural effusions
   4. Severity-of-illness scoring systems in CAP
      a. CURB-65 (Tables 1 and 2)

Table 1. CURB-65 Scoring

CURB-65[a]	
Symptom	**Points**
Confusion	1
BUN > 19 mg/dL	1
Respiratory rate ≥ 30 breaths/minute	1
SBP < 90 mm Hg, DBP ≤ 60 mm Hg	1
Age ≥ 65 yr	1

[a]CRB-65 (without a blood urea nitrogen concentration) is useful in a primary practice setting.
BUN = blood urea nitrogen; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Table 2. CURB-65 Location of Therapy

CURB-65		
Score	**Risk of Death at 30 Days (%)**	**Location of Therapy**
0	0.7	Outpatient
1	2.1	Outpatient
2	9.2	Outpatient or inpatient
3	14.5	Inpatient (± ICU)
4	40.0	Inpatient (± ICU)
5	57.0	Inpatient (± ICU)

ICU = intensive care unit.

b. Pneumonia severity index (or Pneumonia Patient Outcomes Research Team score)
   i. Evaluates 20 patient characteristics
   ii. Assesses risk of mortality, similar to CURB-65
   iii. Has predictive ability similar to that of CURB-65 but better in patients with lower mortality risk

C. HAP and VAP
   1. HAP: Pneumonia in a nonventilated patient that occurs 48 hours or more after admission and was not incubating at the time of admission
   2. VAP: Pneumonia that arises more than 48 hours after endotracheal intubation
   3. Risk factors for hospital-acquired pneumonia
      a. Intubation and mechanical ventilation
      b. Supine patient position
      c. Enteral feeding
      d. Oropharyngeal colonization
      e. Stress ulcer prophylaxis
      f. Blood transfusion
      g. Hyperglycemia
      h. Immunosuppression or corticosteroids
      i. Surgical procedures: thoracoabdominal, upper abdominal, thoracic
      j. Immobilization
      k. Nasogastric tubes
      l. Previous antibiotic therapy

m. Admission to the intensive care unit
n. Advanced age
o. Underlying chronic lung disease

D. Microbiology (Table 3)

Table 3. Incidence of Pneumonia by Organism

Community Acquired (%)		Hospital Acquired (%)	
Unidentifiable	40–60	Unidentifiable	50
Mycoplasma pneumoniae	13–37	*S. aureus*	10
Streptococcus pneumoniae	9–20	*Pseudomonas aeruginosa*	8
Haemophilus influenzae	3–10	*Enterobacter* spp.	5
Chlamydia pneumoniae	1–17	*K. pneumoniae*	4
Legionella pneumophila	0.7–13	*Candida* spp.	3
Viruses	Common	*Acinetobacter* spp.	2
Others:	Uncommon	*Serratia marcescens*	2
Staphylococcus aureus		*Escherichia coli*	2
Moraxella catarrhalis		*S. pneumoniae*	1
Anaerobes			
Gram-negative bacilli (e.g., *Klebsiella pneumoniae*)			
Specific populations in community-acquired pneumonia:		Issues in hospital-acquired pneumonia:	
Alcoholism: *S. pneumoniae,* oral anaerobes, gram-negative bacilli (e.g., *Klebsiella*)		*P. aeruginosa* is transmitted by health care workers' hands or respiratory equipment	
Nursing home: *S. pneumoniae, H. influenzae,* gram-negative bacilli, *S. aureus*		*S. aureus* is transmitted by health care workers' hands	
COPD: *S. pneumoniae, H. influenzae, M. catarrhalis*		Enterobacteriaceae endogenously colonize hospitalized patients' airways (healthy people seldom have gram-negative upper airway colonization)	
Postinfluenza: *H. influenzae, S. aureus, S. pneumoniae*			
Exposure to water: *Legionella*		Stress changes respiratory epithelial cells so that gram-negative organisms can adhere	
Poor oral hygiene: oral anaerobes			
HIV infection: *Pneumocystis jirovecii, S. pneumoniae, M. pneumoniae, Mycobacterium*		Up to 70% of patients in the intensive care unit have gram-negative upper airway colonization, and 25% of them become infected through aspiration	

COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus.

Patient Case

1. R.L. is a 68-year-old man who presents to the emergency department with coughing and shortness of breath. His symptoms, which began 4 days ago, have worsened during the past 24 hours. He is coughing up yellow-green sputum, and he has chills, with a temperature of 102.4°F (39°C). His medical history includes coronary artery disease with a myocardial infarction 5 years ago, congestive heart failure, hypertension, and osteoarthritis. He rarely drinks alcohol and has not smoked since his myocardial infarction. He lives at home with his wife. His medications on admission include lisinopril 10 mg/day, hydrochlorothiazide 25 mg/day, and acetaminophen 650 mg four times/day. On physical examination, he is alert and oriented, with the following vital signs: temperature 101.8°F (38°C), heart rate 100 beats/minute, respiratory rate 32 breaths/minute, and blood pressure 142/94 mm Hg. His laboratory results are normal except for blood urea nitrogen (BUN) 32 mg/dL (serum creatinine [SCr] 1.23 mg/dL). A chest radiograph reveals infiltrates in the right lower lobe. A sputum specimen is not available. If R.L. were hospitalized, which would be the best empiric therapy for him?

   A. Ampicillin/sulbactam 1.5 g intravenously every 6 hours.

   B. Piperacillin/tazobactam 4.5 g intravenously every 6 hours plus gentamicin 180 mg intravenously every 12 hours.

   C. Ceftriaxone 1 g intravenously every 24 hours plus azithromycin 500 mg intravenously every 24 hours.

   D. Doxycycline 100 mg intravenously every 12 hours.

E. Therapy: Pneumonia
   1. CAP
      a. Empiric treatment of nonhospitalized patients
         i. No comorbidities or risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*
            (a) Amoxicillin
            (b) Doxycycline
            (c) Macrolide (clarithromycin or azithromycin) if local pneumococcal resistance to macrolides is less than 25%.
         ii. Comorbidities (chronic obstructive pulmonary disease [COPD], diabetes mellitus, alcoholism, chronic renal or liver failure, congestive heart failure, malignancy, asplenia, or immunosuppression)
            (a) Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg])
            (b) Macrolide or doxycycline with amoxicillin/clavulanate or cefpodoxime or cefuroxime
      b. Empiric treatment of hospitalized patients with non-severe pneumonia (may need to add other antibiotics if the patient has risk factors for Pseudomonas aeruginosa or MRSA)
         i. Respiratory fluoroquinolone (moxifloxacin, or levofloxacin [750 mg])
         ii. Ampicillin/sulbactam, ceftriaxone, or ceftaroline plus a macrolide (or doxycycline)
      c. Empiric treatment of hospitalized patients with severe pneumonia necessitating intensive care unit treatment (may need to add other antibiotics if the patient has risk factors for *P. aeruginosa* or methicillin-resistant *S. aureus* [MRSA])
         i. Ampicillin/sulbactam plus either a respiratory fluoroquinolone or a macrolide
         ii. Ceftriaxone plus either a respiratory fluoroquinolone or a macrolide
         iii. Ceftaroline plus either a respiratory fluoroquinolone or a macrolide
      d. Treatment duration: At least 5 days; duration should be guided by a validated measure of clinical stability (resolution of vital sign abnormalities, ability to eat, and normal mentation)

2. CAP and Risk Factors for MRSA or *P. aeruginosa*
   a. Treat with CAP guideline regimens.
   b. Additional antibiotics with MRSA activity
      i. Include if prior respiratory isolation of MRSA
      ii. Include if patient has locally validated risk factors for MRSA (especially hospitalization and parenteral antibiotics given in past 90 days)
      iii. Vancomycin or linezolid.
   c. Additional antibiotics with *Pseudomonas* activity
      i. Include if prior respiratory isolation of *P. aeruginosa*
      ii. Include if patient has locally validated risk factors for *P. aeruginosa* (especially hospitalization and parenteral antibiotics given in past 90 days).
      iii. Piperacillin/tazobactam, cefepime, ceftazidime, imipenem, meropenem, aztreonam
   d. In lieu of locally validated risk factors, can use the Drug Resistance in Pneumonia (DRIP) score
   e. Therapy with additional antibiotics should be de-escalated on the basis of culture results, nasal PCR for MRSA, and clinical improvement.

Patient Case

2. B.P. is a 66-year-old woman who underwent a two-vessel coronary artery bypass graft 8 days ago and has been on a ventilator in the surgical intensive care unit since then. Her temperature is now rising and her chest radiograph reveals a new infiltrate in the right lower lobe. Her medical history includes coronary artery disease with a myocardial infarction 2 years ago, COPD, and hypertension. All antipseudomonal antibiotics in the institution are active against at least 90% of strains. B.P. has no known drug allergies. Which is the best empiric therapy for B.P.?

   A. Ceftriaxone 1 g intravenously every 24 hours plus gentamicin 7 mg/kg intravenously every 24 hours plus linezolid 600 mg intravenously every 12 hours.

   B. Piperacillin/tazobactam 4.5 g intravenously every 6 hours.

   C. Levofloxacin 750 mg intravenously every 24 hours plus linezolid 600 mg intravenously every 12 hours.

   D. Cefepime 2 g intravenously every 8 hours plus tobramycin 7 mg/kg intravenously every 24 hours plus vancomycin 15 mg/kg intravenously every 12 hours.

3. VAP
   a. Empiric regimen should include antibiotics with activity against *S. aureus* (MSSA), *P. aeruginosa*, and other gram-negative organisms.
   b. Options for single agents: Piperacillin/tazobactam, cefepime, levofloxacin, imipenem, or meropenem.
   c. Two antibiotics with activity against *P. aeruginosa* should be included if the patient has risk factors for MDR organisms (see below) or if *P. aeruginosa* resistance in the hospital unit to the antibiotic considered for monotherapy is greater than 10%. In addition, use two agents for patients with structural lung disease (bronchiectasis or cystic fibrosis).
      i. Options for first agent: Antipseudomonal β-lactam (ceftazidime, cefepime, imipenem, meropenem, piperacillin/tazobactam, or aztreonam). Ceftazidime and aztreonam only if an antibiotic with MRSA activity is also being used.
      ii. Options for second agent: Aminoglycoside, fluoroquinolone (ciprofloxacin, levofloxacin) or colistin (aztreonam may be used with another β-lactam if no other second option is available)

d. An antibiotic with activity against MRSA should be included if the patient has risk factors for MDR organisms (see below) or if MRSA incidence in the hospital unit is greater than 10%–20%. Note: In locations where the prevalence of MRSA respiratory infections is low (< 10%), a negative MRSA nasal screen suggests that MRSA antibiotics are unnecessary empirically. Locations with a high prevalence of MRSA respiratory infections should follow the rule above.
    i. Options if MRSA activity necessary: Vancomycin or linezolid
    ii. If an MRSA agent is used, then ceftazidime and aztreonam are potential alternative choices for the antipseudomonal agent.
e. Ideally, dose antibiotics based on pharmacokinetic/pharmacodynamic data, including antibiotic serum concentrations, extended infusions of β-lactams and weight-based dosing of aminoglycosides
f. Antibiotics should be de-escalated on the basis of culture results. Antibiotic therapy for *P. aeruginosa* can be de-escalated to one active agent on the basis of culture and sensitivity results. Antibiotic therapy for MRSA can be de-escalated/discontinued on the basis of nasal PCR for MRSA results.
g. Treatment duration: 7-day course is recommended for most infections.
h. Risk factors for MDR organisms
    i. Intravenous antibiotic therapy within the past 90 days
    ii. Hospitalization of 5 days or more (VAP only)
    iii. Septic shock at time of VAP (VAP only)
    iv. Acute respiratory distress syndrome preceding VAP (VAP only)
    v. Acute renal replacement therapy before VAP (VAP only)

4. HAP
    a. Empiric regimen should include antibiotics with activity against *S. aureus* (MSSA), *P. aeruginosa*, and other gram-negative organisms.
    b. Options for single agents: Piperacillin/tazobactam, cefepime, levofloxacin, imipenem, or meropenem.
    c. Two antibiotics with activity against *P. aeruginosa* should be included if the patient has received antibiotics in the past 90 days or has a high risk of mortality (indicated by the need for ventilator support or septic shock due to HAP). In addition, use two agents for patients with structural lung disease (bronchiectasis or cystic fibrosis).
        i. Options for first agent: Antipseudomonal β-lactam (ceftazidime, cefepime, imipenem, meropenem, piperacillin/tazobactam, or aztreonam)
        ii. Options for second agent: Aminoglycoside, fluoroquinolone (ciprofloxacin, levofloxacin), or colistin (aztreonam may be used with another β-lactam if no other second option is available)
        iii. Aminoglycosides should not be used as monotherapy.
    d. An antibiotic with activity against MRSA should be included if the patient has risk factors for MDR organisms, if MRSA incidence in the hospital unit is greater than 10%–20%, or if the patient is at a high mortality risk. See statement in VAP section regarding MRSA nasal screening.
        i. Options if MRSA activity necessary: Vancomycin or linezolid
        ii. If an MRSA agent is used, then ceftazidime and aztreonam are potential alternative choices for the antipseudomonal agent.
        iii. Use oxacillin, nafcillin, or cefazolin for proven MSSA infections.
    e. Ideally, dose antibiotics according to pharmacokinetic/pharmacodynamic data, including antibiotic serum concentrations, extended infusions of β-lactams, and weight-based dosing of aminoglycosides.
    f. Antibiotics should be de-escalated according to culture results. Antibiotic therapy for *P. aeruginosa* can be de-escalated to one active agent on the basis of culture and sensitivity results. Antibiotic therapy for MRSA can be de-escalated/discontinued on the basis of nasal PCR for MRSA results.
    g. Treatment duration: A 7-day course is recommended for most infections.

F. Antibiotic Resistance
   1. Innate resistance – Based on characteristics of the microorganism (e.g., *P. aeruginosa* has innate resistance to vancomycin)
   2. Acquired resistance
      a. Mutations – Chromosomal alterations passed to daughter cells only
      b. Horizontal gene transfer
         i. Plasmids – Extrachromosomal DNA that codes for resistance; mobile; can code for resistance to multiple antibiotics
         ii. Transposons – Resistance genes transferred within or between chromosomal DNA or plasmids
         iii. Integrons – DNA component that contains a site where a gene cassette that codes for resistance can be integrated into the bacterial DNA
   3. Mechanisms of resistance
      a. Decreased uptake
         i. β-Lactams
         ii. Fluoroquinolones
         iii. Aminoglycosides (especially *Pseudomonas*)
      b. Enzyme modification and degradation
         i. β-Lactamases (see Table 4)
         ii. Aminoglycoside hydrolytic enzymes (e.g., acetyltransferase, phosphotransferase, adenyl transferase) – Enteric gram-negative bacteria
      c. Altered target site
         i. β-Lactams (e.g., altered penicillin-binding proteins (PBPs), *mecA*) – *Staphylococcus*, *Streptococcus*, and *Enterococcus*
         ii. Glycopeptides (e.g., *vanA* and *vanB*) – Vancomycin resistance in *Enterococcus*
         iii. Fluoroquinolones (e.g., *gyrA* and *parC* mutations)
         iv. Ribosomal mutations (e.g., macrolides, tetracyclines)
         v. Sulfonamides (e.g., altered genes encoding dihydropteroate synthase)
         vi. Trimethoprim (e.g., altered genes encoding dihydrofolate reductase or overproduction of dihydrofolate reductase)
      d. Efflux pumps
         i. Macrolides (e.g., *mef*-encoded efflux in *Streptococcus*)
         ii. Fluoroquinolones
         iii. Tetracyclines

Table 4. β-Lactamases

Molecular Class	Category Name	Target	Examples	Effective Inhibitors
A	Serine β-lactamases	Penicillins, cephalosporins, aztreonam, carbapenems	TEM family; SHV family; CTX-M family; most ESBLs; CRE (KPC)	Avibactam, relebactam, vaborbactam ±clavulanic acid, ±sulbactam, ±tazobactam
B	Metallo β-lactamases	Carbapenems	IMP family, VIM family; CRE (NDM-1)	None
C	Serine β-lactamases	Cephalosporins	Amp C	Avibactam, relebactam, vaborbactam
D	Serine β-lactamases	Extended-spectrum cephalosporins, carbapenems	CRE (OXA family)	Avibactam; ±clavulanic acid; ±tazobactam

CRE = carbapenem-resistant Enterobacteriaceae; CTX-M = cefotaximase, Munich; ESBL = extended-spectrum β-lactamase; IMP = imipenemase; KPC = *Klebsiella pneumoniae* carbapenemase; NDM = New Delhi metallo-β-lactamase; OXA = oxacillinase; VIM = Verona integron-encoded metallo-β-lactamase.

G. Influenza
   1. Characteristics of influenza infection
      a. Epidemic with significant mortality
      b. Epidemics begin abruptly → peak in 2–3 weeks → resolve in 5–6 weeks.
      c. Occurs almost exclusively in the winter
      d. Average overall attack rates of 10%–20%
      e. Mortality greatest in those older than 65 years (especially with heart and lung disease): More than 80% of deaths caused by influenza are from this age group (20,000 deaths a year in the United States).
   2. Is it a cold or the flu? (Table 5)

Table 5. Differentiating the Symptoms of Cold and Influenza

Signs and Symptoms	Influenza	Cold
Onset	Sudden	Gradual
Temperature	Characteristic, high (> 101°F [38°C]) of 3–4 days' duration	Occasional
Cough	Dry; can become severe	Hacking
Headache	Prominent	Occasional
Myalgia (muscle aches and pains)	Usual; often severe	Slight
Tiredness and weakness	Can last 2–3 wk	Very mild
Extreme exhaustion	Early and prominent	Never
Chest discomfort	Common	Mild to moderate
Stuffy nose	Sometimes	Common
Sneezing	Sometimes	Usual
Sore throat	Sometimes	Common

3. Pathophysiology
    a. Type A
        i. Influenza further grouped by variations in hemagglutinin and neuraminidase (e.g., H1N1, H3N2)
        ii. Changes through antigenic drift or shift
            (a) Drift: Annual, gradual change caused by mutations, substitutions, and deletions
            (b) Shift: Less common dramatic change leading to pandemics
        iii. Causes epidemics every 1–3 years
    b. Type B
        i. Type B influenza carries one form of hemagglutinin and one form of neuraminidase, both of which are less likely to mutate than the hemagglutinin and neuraminidase of type A influenza.
        ii. Changes through antigenic drift (minor mutations from year to year); when enough drifts occur, an epidemic is likely.
        iii. Causes epidemics every 5 years
4. Therapy
    a. Treatment indicated in patients with confirmed or suspected influenza and the following conditions (use only the neuraminidase inhibitors):
        i. Hospitalized patients
        ii. Outpatients with severe or progressive illness
        iii. Outpatients at high risk of influenza complications
            (a) Patients younger than 2 years or 65 years and older
            (b) Patients with chronic disease states: Pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions
            (c) Immunosuppressed patients
            (d) Pregnant women and those within 2 weeks postpartum
            (e) Patients younger than 19 years who are receiving long-term aspirin therapy
            (f) American Indians and Alaska Natives
            (g) Patients who are morbidly obese
            (h) Residents of nursing homes and other long-term care facilities
        iv. Treatment may be considered for those without risk factors including:
            (a) Outpatients with illness onset less than 48 hours
            (b) Symptomatic outpatients who are household contacts of individuals at high risk of complications
            (c) Symptomatic health care providers who are caregivers for individuals at high risk of complications, including:
                (1) Outpatients with illness onset less than 48 hours
                (2) Symptomatic outpatients who are household contacts of individuals at high risk of complications
                (3) Symptomatic health care providers who are caregivers for individuals at high risk of complications
    b. Adamantanes
        i. Amantadine, rimantadine
        ii. Inhibit viral uncoating and release of viral nucleic acid by inhibiting M2 protein
            (a) Never effective against influenza B virus
            (b) Not recommended for treatment because of current universal resistance in influenza A

c. Neuraminidase inhibitors
    i. Oseltamivir, zanamivir, peramivir
    ii. Inhibit neuraminidase; symptoms resolve 1–1.5 days sooner
    iii. Adverse effects
        (a) Oseltamivir: Gastrointestinal (GI) (nausea and vomiting), central nervous system (CNS) (anxiety, headache, insomnia, etc.)
        (b) Zanamivir: Bronchospasm, cough (not recommended in patients with asthma or COPD)
        (c) Peramivir: Diarrhea; aspartate aminotransferase, alanine aminotransferase, creatinine phosphokinase, glucose elevation
    iv. Dosage
        (a) Oseltamivir: 75 mg orally twice daily for 5 days; decrease dosage to 30 mg twice daily orally in patients with a creatinine clearance (CrCl) of 31–60 mL/minute/1.73 m^2 and 30 mg once daily orally in patients with a CrCl of 11–30 mL/minute/1.73 m^2.
        (b) Zanamivir: Two inhalations (5 mg/inhalation) twice daily for 5 days
        (c) Peramivir: 600 mg intravenously once; decrease dose to 200 and 100 mg in patients with a CrCl less than 50 and 30 mL/minute/1.73 m^2, respectively
        (d) Initiate within 48 hours of symptom onset.
d. Endonuclease inhibitors
    i. Baloxavir
    ii. Inhibits viral endonuclease which is vital for initiating viral transcription; symptoms resolve 1-1.5 days sooner
    iii. Adverse effects: gastrointestinal, bronchitis, headache (all similar to placebo)
    iv. Dosage: 40 mg once (40-79 kg) or 80 mg once (> 80 kg)

5. Prevention
    a. Prophylaxis in the community
        i. Patients at very high risk of developing complications when influenza vaccination is contraindicated or for whom the vaccine is expected to have low effectiveness. Use for the duration of influenza activity.
        ii. Hematopoietic stem cell or lung transplant recipients. Use for the duration of influenza activity.
        iii. Patients at high risk of complications or people in close contact with these patients. Use short term and give vaccine.
    b. Prophylaxis for institutional outbreaks
        i. All exposed residents or patients in outbreak-affected units regardless of influenza vaccination history
        ii. Unvaccinated or recently vaccinated caregivers
        iii. Use prophylaxis for at least 14 days and continue for 7 days after the last identified case in the institution.
    c. Amantadine, rimantadine: Not recommended for prevention because of current universal resistance
    d. Use neuraminidase inhibitors only: Oseltamivir 75 mg/day orally

Patient Case

3. S.C. is a 46-year-old woman who presents to the clinic with purulent nasal discharge, nasal and facial congestion, headaches, fever, and dental pain. Her symptoms began about 10 days ago, improved after about 4 days, and then worsened again a few days later. Which is the best empiric therapy for S.C.?

   A. Cefpodoxime proxetil 200 mg orally twice daily.

   B. Clindamycin 300 mg orally four times daily.

   C. Amoxicillin/clavulanate 875 mg/125 mg orally twice daily.

   D. No antibiotic therapy needed because this is a typical viral infection.

H. Sinusitis

1. Definition and etiology
   a. Inflammation of the mucosal lining of the nasal passage and paranasal sinuses lasting up to 4 weeks
   b. Many different causes, including viruses, bacteria, and fungi
   c. Viruses account for more than 90% of cases, whereas bacteria account for less than 10%.
2. Diagnosis
   a. Presence of at least two major symptoms or one major and two or more minor symptoms (Table 6)

Table 6. Symptoms Associated with Diagnosis of Sinusitis

Major Symptoms	Minor Symptoms
Purulent anterior nasal discharge	Headache
Purulent or discolored posterior nasal discharge	Ear pain, pressure, or fullness
Nasal congestion or obstruction	Halitosis
Facial congestion or fullness	Dental pain
Facial pain or pressure	Cough
Hyposmia or anosmia	Fever (for subacute or chronic sinusitis)
Fever (for acute sinusitis only)	Fatigue

   b. Viral or bacterial? (Table 7)

Table 7. Differentiating Viral from Bacterial Sinusitis

Characteristics	Viral	Bacterial
Symptoms	Nasal discharge, congestion, and scratchy throat	Nasal discharge, congestion, and scratchy throat
Nasal discharge	Clear to purulent to clear; purulence not present until days 4–5	Persistent purulent discharge (> 10 days) *or* early and severe (first 3–4 days) *or* increased on days 5–6 after typical viral infection ("double-sickening")
Fever	None (or early in course, resolving in 48 hr)	High temperature (≥ 102.2°F [39°C]) and early (first 3–4 days)
Other symptoms	Headache, facial pain, and myalgia (resolving in 48 hr)	Headache, facial pain, myalgia, daytime cough
Peak symptoms	Days 3–6	Persistent > 10 days *or* early and severe (first 3–4 days) *or* improved symptoms that worsen on days 5–6
Duration	5–10 days	In general, > 10 days

3. Treatment
    a. Begin antibiotics as soon as *bacterial* sinusitis is diagnosed (see criteria in Table 7).
    b. First-line therapy
        i. Amoxicillin/clavulanate
        ii. High-dose amoxicillin/clavulanate (2 g /125 mg twice daily in adults or 90/6.435 mg/kg/day divided twice daily) in:
            (a) Geographic regions with high endemic rates (greater than 10%) of invasive penicillin-nonsusceptible *S. pneumoniae*
            (b) Those with a severe infection (e.g., evidence of systemic toxicity with a temperature of 102.2°F (39°C) or higher and a threat of suppurative complications)
            (c) Attendance at day care
            (d) Age younger than 2 years or older than 65 years
            (e) Recent hospitalization
            (f) Antibiotic use within the past month
            (g) Those who are immunocompromised
    c. Second-line therapy
        i. Respiratory fluoroquinolone (including children with type I hypersensitivity to penicillin) – Because of serious adverse effects, avoid if there are other treatment options.
        ii. Doxycycline
        iii. Cefixime or cefpodoxime proxetil with clindamycin (for children with non–type I hypersensitivity to penicillin)
        iv. Intranasal saline irrigation as adjunctive therapy
        v. Intranasal corticosteroids as adjunctive therapy in patients with allergic rhinitis
    d. Therapy duration
        i. Adults: 5–7 days
        ii. Children: 10–14 days

II. URINARY TRACT INFECTIONS

A. Introduction
1. Most common bacterial infection in humans: 7 million office visits per year; 1 million hospitalizations
2. Many women (15%–20%) will have a urinary tract infection (UTI) during their lifetime
3. 1–50 years of age: UTIs occur predominantly in women; after 50: men are increasingly affected because of prostate problems

B. Microbiology (Table 8)

Table 8. Incidence of Urinary Tract Infections by Organism

Community Acquired (%)		**Nosocomial (%)**	
Escherichia coli	73	*E. coli*	31
Staphylococcus saprophyticus	13	*Pseudomonas aeruginosa*	10
Proteus mirabilis	5	Other gram-negative bacilli	10
Klebsiella pneumoniae	4	*K. pneumoniae*	9
Enterococcus	2	*Staphylococcus aureus*	6
		P. mirabilis	5
		Enterococcus	2
		Fungal	14

C. Predisposing Factors
   1. Age
   2. Female sex
   3. Diabetes mellitus
   4. Pregnancy
   5. Immunosuppression
   6. Urinary tract instrumentation
   7. Urinary tract obstruction
   8. Renal disease, renal transplantation
   9. Neurologic dysfunction

Patient Case

4. G.N. is a 62-year-old woman who presents to the emergency department with a 3-day history of urinary frequency and dysuria. During the past 24 hours, she has had nausea, vomiting, and flank pain. G.N. has a history of type 2 diabetes, which is poorly controlled, with some diabetes-related complications. G.N. also has hypertension and a history of several episodes of deep venous thrombosis. Her medications include glyburide 5 mg orally daily, enalapril 10 mg orally twice daily, warfarin 3 mg orally daily, and metoclopramide 10 mg orally four times daily. On physical examination, she is alert and oriented, with the following vital signs: temperature 102.8°F (39°C), heart rate 120 beats/minute, respiratory rate 16 breaths/minute, supine blood pressure 140/75 mm Hg, and standing blood pressure 110/60 mm Hg. Her laboratory values are within normal limits except for elevated international normalized ratio 2.7, BUN 26 mg/dL, SCr 1.88 mg/dL, and WBC 12,000 cells/mm^3 (78 polymorphonuclear leukocytes, 7 band neutrophils, 10 lymphocytes, and 5 monocytes). Her urinalysis reveals turbidity, 2+ glucose, pH 7.0, protein 100 mg/dL, 50–100 WBCs, positive nitrites, 3–5 red blood cells, and many bacteria and positive for casts. Which is the best empiric therapy for G.N.?

   A. Trimethoprim/sulfamethoxazole double strength orally twice daily for 7 days. Monitor INR carefully.

   B. Ciprofloxacin 400 mg intravenously twice daily and then 500 mg orally twice daily for a total of 7 days. Monitor INR carefully.

   C. Gentamicin 140 mg intravenously every 24 hours for 3 days.

   D. Tigecycline 100 mg once, then 50 mg intravenously every 12 hours and then doxycycline 100 mg orally twice daily for a total of 10 days.

D. Clinical Presentation
   1. Lower UTI: Cystitis (older adults may have only nonspecific symptoms, such as mental status changes, abdominal pain, and decreased eating or drinking)
      a. Dysuria
      b. Frequent urination
      c. Urgency
      d. Occasionally, gross hematuria
   2. Upper UTI: Pyelonephritis (older adults may have only nonspecific symptoms, such as mental status changes, abdominal pain, and decreased eating or drinking)
      a. Frequency, dysuria, hematuria
      b. Suprapubic pain
      c. Costovertebral angle tenderness; flank pain
      d. Fever, chills
      e. Elevated WBC
      f. Nausea, vomiting

3. Factors associated with or used to define complicated UTI (UTI involving a structural or functional abnormality)
    a. Male sex
    b. Hospital acquired
    c. Pregnancy
    d. Anatomic abnormality of the urinary tract
    e. Poorly controlled diabetes mellitus
    f. Recent antimicrobial use
    g. Indwelling urinary catheter
    h. Recent urinary tract instrumentation
    i. Immunosuppression
4. Recurrent cystitis
    a. Relapse: Infection with the same organism within 14 days of discontinuing antibiotics for the preceding UTI
    b. Reinfection: Infection with a completely different organism; most common cause of recurrent cystitis

E. Diagnosis: Urinalysis (blood cultures will be positive in 20% of patients with upper UTIs)
1. Pyuria (WBC greater than 10 cells/mm^3)
2. Bacteriuria (more than 10^2 colony-forming units per milliliter is diagnostic) in symptomatic patients or those with catheters
3. Red blood cells
4. Cloudiness
5. Nitrite positive (*E. coli, Proteus, Klebsiella*)
6. Leukocyte esterase positive
7. Casts (if pyelonephritis)
8. Note: patient must also have symptoms; diagnosis cannot be made on urinalysis results alone.

F. Asymptomatic Bacteriuria
1. Asymptomatic bacteriuria should only be screened for and treated in pregnant women and patients undergoing endoscopic urologic procedures.
    a. Pregnant women should be treated for 4–7 days.
    b. Patients undergoing endoscopic urologic procedures should be treated with one or two doses of antibiotics.
2. Patients with functional and/or cognitive impairment should not be treated for asymptomatic bacteriuria solely on the basis of a history of falls or mental status changes/confusion. Patients must have local urinary symptoms or systemic signs of infection.

G. Therapy
1. Uncomplicated cystitis
    a. Recommended therapy
        i. Trimethoprim/sulfamethoxazole 160 mg/800 mg twice daily for 3 days. Avoid if resistance prevalence is known to exceed 20% or if used for UTI in previous 3 months.
        ii. Nitrofurantoin monohydrate/macrocrystals 100 mg twice daily for 5 days (ineffective in patients with a CrCl less than 30 mL/minute/1.73 m^2)
        iii. Fosfomycin tromethamine 3 g, one dose

   b. Alternatives
      i. Fluoroquinolones (not moxifloxacin) for 3 days – Because of serious adverse effects, avoid fluoroquinolones if there are other treatment options.
      ii. β-Lactams (amoxicillin-clavulanate, cefdinir, cefaclor, cephalexin, and cefpodoxime proxetil) for 5–7 days
2. Uncomplicated pyelonephritis
   a. Outpatient therapy (if patient is not immunocompromised or does not have nausea and vomiting)
      i. Trimethoprim/sulfamethoxazole 160 mg/800 mg twice daily for 14 days
      ii. Levofloxacin 750 mg orally daily for 5 days or ciprofloxacin 500 mg orally twice daily for 7 days (not moxifloxacin) – Because of serious adverse effects, avoid fluoroquinolones if there are other treatment options.
      iii. β-Lactams (see above) for 10–14 days (less effective than first two options)
   b. Uropathogen resistance greater than 10%: Use initial dose of an intravenous, long-acting β-lactam (e.g., ceftriaxone) or once-daily aminoglycoside.
3. Complicated UTIs
   a. Outpatient therapy
      i. Trimethoprim/sulfamethoxazole 160 mg/800 mg twice daily for 7-14 days
      ii. Levofloxacin 750mg oral daily for 5 days or ciprofloxacin 500mg oral twice daily for 7 days (not moxifloxacin)
      iii. β-Lactams (see above) for 7–14 days
   b. Inpatient therapy
      i. Fluoroquinolone
      ii. Aminoglycoside
      iii. Ceftriaxone (consider a β-lactam with antipseudomonal activity in patients recently hospitalized or with urinary catheters or living in nursing homes)
      iv. Therapy duration: 5–14 days (5 days with levofloxacin)
4. Pregnancy (pregnant women should be screened for bacteriuria and treated, even if asymptomatic)
   a. Antibiotic options
      i. Amoxicillin/clavulanate for 3-5 days
      ii. Nitrofurantoin (avoid in the first trimester and at term if other options available) for 5 days
      iii. Cephalexin or cefpodoxime proxetil for 3-5 days
      iv. Fosfomycin tromethamine single dose
   b. Antibiotics to avoid
      i. Fluoroquinolones
      ii. Tetracyclines
      iii. Aminoglycosides
      iv. Trimethoprim/sulfamethoxazole (used frequently but avoidance recommended, especially during the late third trimester)
5. Recurrent cystitis
   a. Relapse
      i. Assess for pharmacologic reason for treatment failure.
      ii. Longer treatment (for 2–6 weeks, depending on length of initial course)

b. Reinfection (reassess need for continuous prophylactic antibiotics every 6–12 months)
    i. If patient has two or fewer UTIs in 1 year, use patient-initiated therapy for symptomatic episodes (3-day treatment regimens).
    ii. If patient has three or more UTIs in 1 year and they are temporally related to sexual activity, use postintercourse prophylaxis with trimethoprim/sulfamethoxazole single strength, cephalexin 250 mg, or nitrofurantoin 50–100 mg and counsel on voiding after intercourse.
    iii. If patient has three or more UTIs in 1 year that are not related to sexual activity, use daily or three times per week prophylaxis with trimethoprim 100 mg, trimethoprim/sulfamethoxazole single strength, cephalexin 250 mg, or nitrofurantoin 50–100 mg.

6. Catheter-related UTIs
    a. Short-term indwelling catheters
        i. Risk of bacteriuria is 5% for each day of catheterization.
        ii. By 30 days, 75%–95% of patients with an indwelling catheter will have bacteriuria.
        iii. Preventive antimicrobial therapy is not recommended; it only increases the chance of selecting out resistant organisms.
        iv. Asymptomatic patients with bacteriuria should not be treated.
        v. Symptomatic patients with bacteriuria should be treated with 7 days of antibiotics if symptoms resolve promptly and with 10–14 days of antibiotics if there is a delayed response (both durations whether or not catheter removed). Treat for 5 days with levofloxacin if the patient is not severely ill; treat for 3 days in women 65 years and younger who have their catheters removed and who do not have upper urinary tract symptoms.
        vi. The most common organisms are *E. coli* (21.4%), *Candida* spp. (21.0%), *Enterococcus* spp. (14.9%), *P. aeruginosa* (10.0%), *K. pneumoniae* (7.7%), and *Enterobacter* spp. (4.1%).
    b. Long-term indwelling catheters
        i. Almost all patients will be bacteriuric with two to five organisms.
        ii. Asymptomatic patients should not be treated. Catheters do not need to be replaced.
        iii. Symptomatic patients should be treated for a short period (7 days) to prevent resistance, and catheter replacement may be indicated.

7. Prostatitis and epididymitis
    a. Acute bacterial prostatitis
        i. Primarily gram-negative organisms
        ii. Therapy duration, 2–4 weeks – can be extended for an additional 2 weeks if patient remains symptomatic
            (a) Trimethoprim/sulfamethoxazole
            (b) Fluoroquinolones
    b. Chronic bacterial prostatitis
        i. Difficult to treat
        ii. Therapy duration, 1–4 months
            (a) Trimethoprim/sulfamethoxazole
            (b) Fluoroquinolones

8. Epididymitis
    a. Older than 35 years, probably caused by enteric organisms
        i. Therapy duration: 10 days to 4 weeks
        ii. Antibiotics: trimethoprim/sulfamethoxazole or fluoroquinolones
    b. Younger than 35 years, probably gonococcal or chlamydial infection
        i. Therapy duration: 10 days
        ii. Antibiotics: ceftriaxone 250 mg intramuscularly once plus doxycycline 100 mg twice daily

III. SKIN AND SKIN STRUCTURE INFECTIONS

A. Cellulitis
   1. Description
      a. Acute spreading skin infection that involves primarily the deep dermis and subcutaneous fat
      b. Nonelevated, poorly defined margins
      c. Warmth, pain, erythema and edema, and tender lymphadenopathy
      d. Malaise, fever, and chills
      e. Usually, patient has had previous minor trauma, abrasions, ulcers, or surgery (could be tinea infections, psoriasis, or eczema).
      f. Often, patients have impaired lymphatic drainage.
   2. Microorganism: Usually *Streptococcus pyogenes* and occasionally *S. aureus* (rarely other organisms); blood cultures are rarely positive and not routinely recommended unless severe systemic symptoms are present or the patient is immunosuppressed
   3. Treatment: 5–10 days (may extend therapy if infection has not improved)
      a. Penicillin G if definitively streptococcal
      b. First-generation cephalosporin (cefazolin, cephalexin)
      c. Ceftriaxone
      d. Clindamycin
      e. Treat empirically for MRSA if associated with penetrating trauma, injection drug use, purulent drainage, nasal colonization with MRSA, concurrent evidence of MRSA infection elsewhere or systemic inflammatory response syndrome (SIRS) criteria (severe nonpurulent).
         i. Outpatient: Clindamycin, trimethoprim/sulfamethoxazole (add β-lactam for *Streptococcus*), doxycycline (add β-lactam for *Streptococcus*)
         ii. Inpatient: Vancomycin, linezolid, daptomycin, or telavancin

B. Erysipelas
   1. Description
      a. Acute spreading skin infection that involves primarily the superficial dermis
      b. Spreads rapidly through the lymphatic system in the skin (patients may have impaired lymphatic drainage)
      c. Usually occurs in infants and older adults
      d. Usually occurs on the legs and feet (facial erysipelas can occur, but this is less common)
      e. Warmth, erythema, and pain
      f. Edge of infection is elevated and sharply demarcated from the surrounding tissue.
      g. Systemic signs of infection are common, but blood cultures are positive only 5% of the time.
   2. Microorganism: Group A *Streptococcus* (*S. pyogenes*), but occasionally groups G, C, and B are seen
   3. Treatment: 5 days (may extend therapy if infection has not improved)
      a. Penicillin G
      b. Cefazolin
      c. Clindamycin

C. Necrotizing Fasciitis
   1. Description
      a. Acute, necrotizing cellulitis that involves the subcutaneous fat and superficial fascia
      b. Infection extensively alters surrounding tissue, leading to cutaneous anesthesia or gangrene.
      c. Very painful (pain out of proportion to appearance)
      d. Streptococcal infection: Either spontaneous or attributable to varicella, minor trauma (cuts, burns, and splinters), or surgical procedures
      e. Mixed infection: generally secondary to perianal abscess, abdominal surgery, trauma, decubitus ulcers, or injection sites in persons who inject drugs
      f. Significant systemic symptoms, including shock and organ failure
   2. Microorganisms
      a. Mixed infection with facultative and anaerobic bacteria (Type 1)
      b. *S. pyogenes* (Type 2)
   3. Treatment
      a. Surgical debridement: Most important therapy and often repeated debridement is necessary
      b. Antibiotics are not curative; given in addition to surgery (if used early, may be effective alone)
      c. Empiric therapy: Vancomycin or linezolid plus piperacillin/tazobactam or a carbapenem or ceftriaxone with metronidazole
      d. If group A streptococci, *S. aureus*, or *Clostridium* spp. suspected, clindamycin should be included in the empiric regimen to suppress toxin and cytokine production
      e. Streptococcal necrotizing fasciitis: High-dose intravenous penicillin plus clindamycin

Patient Case

5. G.N. returns to the clinic in 6 months with no urinary symptoms, but her chief concern is now an ulcer on her right foot. She recently returned from a vacation in Florida and thinks she might have stepped on something while walking barefoot on the beach. Her foot is not sore but is red and swollen around the deep ulcer. Her medications are the same as before. Vital signs are stable, and there is nothing significant on physical examination except for the right foot ulcer. Laboratory values are within normal limits (SCr 0.86 mg/dL). Which is the best empiric therapy for G.N.?

   A. Nafcillin 2 g intravenously every 6 hours for 6–12 weeks.

   B. Tobramycin 120 mg intravenously every 12 hours plus levofloxacin 750 mg intravenously every 24 hours for 1–2 weeks.

   C. Ampicillin/sulbactam 3 g intravenously every 6 hours for 2–3 weeks.

   D. Below-the-knee amputation followed by ceftriaxone 1 g intravenously every 24 hours for 1 week.

IV. DIABETIC FOOT INFECTIONS

A. Epidemiology
   1. 25% of people with diabetes develop foot infections.
   2. 1 in 15 needs amputation.

B. Etiology
   1. Neuropathy: Motor and autonomic
      a. Mechanical or thermal injuries lead to ulcerations without patient knowledge.
      b. Gait disturbances and foot deformities; maldistribution of weight on the foot
      c. Diminished sweating, causing dry, cracked skin
   2. Vasculopathy: Decreased lower limb perfusion
   3. Immunologic defects: Cellular and humoral

C. Causative Organisms: In general, polymicrobial (average, 2.1–5.8 microorganisms)
   1. *S. aureus*
   2. Group A and B *Streptococcus*
   3. *Enterococcus*
   4. *Proteus*
   5. *E. coli*
   6. *Klebsiella*
   7. *Enterobacter*
   8. *P. aeruginosa*
   9. *Bacteroides fragilis*
   10. *Peptostreptococcus*

D. Therapy
   1. Preventive therapy
      a. Examine feet daily for calluses, blisters, trauma, and so forth.
      b. Wear properly fitting shoes.
      c. Do not walk barefoot.
      d. Keep feet clean and dry.
      e. Have toenails cut properly.
   2. Antimicrobial therapy
      a. Mild infections (and no antibiotics in the past month), defined as local infection involving only the skin and the subcutaneous tissue, with no SIRS criteria and erythema of 2 cm or less
         i. No MRSA risk factors: Dicloxacillin, nafcillin, cephalexin, cefazolin, levofloxacin, or clindamycin
         ii. MRSA risk factors (see below): Doxycycline or trimethoprim/sulfamethoxazole
      b. Moderate to severe infections, defined as local infection with erythema greater than 2 cm, or involving structures deeper than skin and subcutaneous tissues without (moderate) or with (severe) 2 or more SIRS criteria
         i. Ampicillin/sulbactam
         ii. Ertapenem
         iii. Cefoxitin
         iv. Moxifloxacin alone or ciprofloxacin/levofloxacin plus clindamycin
         v. Tigecycline

vi. If risk of *P. aeruginosa* (uncommon in diabetic foot infections and often a nonpathogenic colonizer), use piperacillin/tazobactam, ceftazidime, cefepime, meropenem, or imipenem. Risk factors for *Pseudomonas* include high local prevalence of *Pseudomonas* infection, warm climate, frequent exposure of the foot to water, a severe infection, and failure of previous therapy with nonpseudomonal antibiotics.

vii. If risk of MRSA, use vancomycin, linezolid, or daptomycin. Risk factors for MRSA include history of MRSA infection or colonization, high local prevalence of MRSA, or a severe infection.

c. Treatment duration: 1–2 weeks for mild infections and 2–3 weeks for moderate to severe infections. Extended duration is needed for osteomyelitis. After amputation, treatment duration is 2–5 days if there is no remaining infected tissue or or bone, 1–3 weeks if residual infected tissue only, and 4–6 weeks if residual infected bone.

E. Surgical Therapy
   1. Drainage and debridement (appropriate wound care) are very important.
   2. Amputation is often necessary; if infection is discovered early, can maintain structural integrity of the foot.

Patient Case

6. W.A. is a 55-year-old man who presents with weight loss, malaise, and severe back pain and spasms that have progressed during the past 2 months. He has also experienced loss of sensation in his lower extremities. Four months before this admission, he had surgery for a fractured tibia, followed by an infection treated with unknown antibiotics. W.A. has hypertension and a history of diverticulitis. On physical examination, he is alert and oriented, with the following vital signs: temperature 99.4°F (37.4°C), heart rate 88 beats/minute, respiratory rate 14 breaths/minute, and blood pressure 130/85 mm Hg. His laboratory values are within normal limits, except for WBC 14,300 cells/mm^3, erythrocyte sedimentation rate 89 mm/hour, and C-reactive protein 12 mg/dL. Magnetic resonance imaging reveals bony destruction of lumbar vertebrae 1 and 2, which is confirmed by a bone scan. A computed tomography–guided bone biopsy reveals gram-positive cocci in clusters. Which is the best therapy for W.A.?

   A. Vancomycin 15 mg/kg intravenously every 12 hours for 6 weeks.

   B. Nafcillin 2 g intravenously every 6 hours for 2 weeks.

   C. Levofloxacin 750 mg orally every 24 hours for 6 weeks.

   D. Ampicillin/sulbactam 3 g intravenously every 6 hours for 2 weeks.

V. OSTEOMYELITIS

A. Introduction
   1. Infection of the bone with subsequent bone destruction
   2. About 20 cases per 100,000 people

B. Characteristics (Table 9)

Table 9. Characteristics of Osteomyelitis

	Hematogenous Spread	Contiguous Spread	Vascular Insufficiency
Definition	Spread of bacteria through the bloodstream from a distant site	Spread of bacteria from an adjacent tissue infection or by direct inoculation	Infection results from insufficient blood supply to fight the bacteria
Patient population	Children (< 16 yr): femur, tibia, humerus Adult: vertebrae	Adults (25–50 yr): femur, tibia, skull	Adults (> 50 yr)
Predisposing factors	Bacteremia (e.g., IV catheters, IVDU, skin infections, URI) Sickle cell anemia	Open reduction of fractures Gunshot wound Dental or sinus infections Soft tissue infections	Diabetes PVD Post-CABG (sternum)
Common pathogens	Usually monomicrobial Children: *Staphylococcus aureus* (60%–90%), *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Enterobacter*, *Escherichia coli* (all < 5%) Adults: *S. aureus* and gram-negative bacilli Sickle cell anemia: *Salmonella* (67%), *S. aureus, S. pneumoniae* IVDU: *P. aeruginosa*	Usually mixed infection: *S. aureus* (60%), *S. epidermidis, Streptococcus* Gram-negative bacilli: *P. aeruginosa* (foot punctures), *Proteus*, *Klebsiella*, *E. coli* Anaerobic (human bites, decubitus ulcers)	Usually polymicrobial: *S. aureus, S. epidermidis, Streptococcus* Gram-negative bacilli Anaerobic (*Bacteroides fragilis* group) Infected prosthesis: *S. aureus, S. epidermidis*

CABG = coronary artery bypass graft; IV = intravenous; IVDU = intravenous drug use; PVD = peripheral vascular disease; URI = upper respiratory infection.

C. Clinical Presentation
   1. Signs and symptoms
      a. Fever and chills
      b. Localized pain, tenderness, and swelling
      c. Neurologic symptoms if spinal cord compression
   2. Laboratory tests
      a. Elevated WBC
      b. Elevated erythrocyte sedimentation rate
      c. Elevated C-reactive protein
   3. Diagnostic tests
      a. Radiographic tests: Positive results lag behind infectious process.
      b. Computed tomography and magnetic resonance imaging scans
      c. Radionuclide imaging: Positive as soon as 24–48 hours after infectious process begins.

D. Empiric Therapy
   1. Pediatric (neonate therapy should be tailored to the patient)
      a. Cefazolin
      b. Nafcillin, oxacillin
      c. Clindamycin (use if prevalence of MRSA in community is 10% or more)
      d. Vancomycin (use if prevalence of MRSA and clindamycin-resistant *S. aureus* in community is 10% or more)

2. Adults
    a. Nafcillin, oxacillin, cefazolin, ceftriaxone, clindamycin, or vancomycin (alternatives linezolid or daptomycin)
    b. Choose additional antibiotics according to patient-specific characteristics.
3. Patients with sickle cell anemia: Ceftriaxone/cefotaxime or ciprofloxacin/levofloxacin (no studies assessing best empiric therapy). Patients are at risk of *Salmonella*.
4. Prosthetic joint infections
    a. Debridement and retention of prosthesis or one-stage exchange of prosthesis
        i. Staphylococcal: Pathogen-specific intravenous therapy plus rifampin 300–450 mg twice daily for 2–6 weeks, followed by rifampin plus ciprofloxacin or levofloxacin for 3 months (hip, elbow, shoulder, ankle prosthesis) or 6 months (knee prosthesis)
        ii. Nonstaphylococcal: Pathogen-specific intravenous (or highly bioavailable oral) therapy for 4–6 weeks, followed by indefinite oral suppression therapy
    b. Resection of prosthesis with or without planned reimplantation or amputation
        i. Pathogen-specific intravenous (or highly bioavailable oral) therapy for 4–6 weeks
        ii. Only 24–48 hours of antibiotic therapy after amputation if all infected tissue is removed

E. Therapy Length
1. Acute osteomyelitis: 4–6 weeks
2. Chronic osteomyelitis: 6–8 weeks of parenteral therapy and 3–12 months of oral therapy

F. Criteria for Effective Oral Therapy for Osteomyelitis
1. Highly bioavailable antibiotic is available.
2. Adherence
3. Identified organism that is highly susceptible to the oral antibiotic used
4. C-reactive protein less than 2.0 mg/dL
5. Adequate surgical debridement
6. Resolving clinical course

VI. CENTRAL NERVOUS SYSTEM INFECTIONS

A. Meningitis: Introduction
1. Incidence: About 8.6 cases per 100,000 people
2. Occurs more often in male than in female patients
3. More common in children

B. Microbiology (Table 10)
   1. Bacterial (septic meningitis)

Table 10. Bacterial Etiology of Meningitis, Based on Age

Age	Most Likely Organisms	Less Common Organisms
< 1 mo (newborns)	*Streptococcus agalactiae* *Listeria monocytogenes* *Streptococcus pneumoniae* *Neisseria meningitidis*	*Escherichia coli*, *Klebsiella* spp. Herpes simplex type 2
1–23 mo	*Streptococcus pneumoniae* *Neisseria meningitidis* *Haemophilus influenzae* *Streptococcus agalactiae*	Viruses *E. coli*
2–50 yr	*N. meningitidis* *S. pneumoniae*	*H. influenzae* Viruses
> 50 yr	*S. pneumoniae* *N. meningitidis* *L. monocytogenes*	*Streptococcus agalactiae*, *H. influenzae*, aerobic gram-negative bacilli, viruses

   2. Other causes (aseptic meningitis)
      a. Viral
      b. Fungal
      c. Parasitic
      d. Tubercular
      e. Syphilis
      f. Drugs (e.g., trimethoprim/sulfamethoxazole, ibuprofen)

C. Predisposing Factors
   1. Head trauma
   2. Immunosuppression
   3. CNS shunts
   4. Cerebrospinal fluid (CSF) fistula or leak
   5. Neurosurgical patients
   6. Alcoholism
   7. Local infections
      a. Sinusitis
      b. Otitis media
      c. Pharyngitis
      d. Bacterial pneumonia
   8. Splenectomized patients
   9. Sickle cell disease
   10. Congenital defects

D. Clinical Presentation
   1. Symptoms
      a. Fever, chills
      b. Headache, backache, nuchal rigidity, mental status changes, photophobia
      c. Nausea, vomiting, anorexia, poor feeding habits (infants)
      d. Petechiae or purpura (*Neisseria meningitidis* meningitis)

2. Physical signs
    a. Brudzinski sign
    b. Kernig sign
    c. Bulging fontanel

E. Diagnosis
1. History and physical examination
2. Blood cultures
3. Lumbar puncture
    a. Elevated opening pressure
    b. Composition in bacterial meningitis (Table 11)

Table 11. CSF Changes in Bacterial Meningitis

Component	Normal CSF	Bacterial Meningitis	Viral Meningitis
Glucose	30–70 mg/dL (2/3 peripheral)	< 50 mg/dL (≤ 0.4 CSF and blood)	Normal
Protein	< 50 mg/dL	> 150 mg/dL	Normal to slightly elevated
WBC	< 5 cells/mm^3	> 1000–5000 cells/mm^3 (predominantly neutrophils)	5–300 cells/mm^3 (predominantly lymphocytes)
pH	7.3	7.1	7.3
Lactic acid	< 14 mg/dL	> 35 mg/dL	< 14 mg/dL

CSF = cerebrospinal fluid.

    c. CSF stains and studies
        i. Gram stain (microorganisms): Helps identify organism in 60%–90% of cases
        ii. Latex agglutination: High sensitivity, 50%–100%, for common organisms
            (a) Not recommended routinely
            (b) Most useful in patients pretreated with antibiotics with subsequent negative CSF Gram stains and cultures
        iii. Polymerase chain reactions (PCR): Detects most common causes of bacterial meningitis; high specificity and sensitivity
        iv. Acid-fast staining (tubercular meningitis)
        v. Cryptococcal antigen
        vi. Herpes simplex virus polymerase chain reaction
4. Laboratory findings
    a. Elevated WBC with a left shift
    b. CSF Gram stain
    c. CSF cultures (positive in 75%–80% of bacterial meningitis cases)
    d. Blood cultures (±)
    e. C-reactive protein concentrations: High negative predictive value

Patient Case

7. D.M. is a 21-year-old university student who presents to the emergency department with the worst headache of his life. During the past few days, he has felt slightly ill but has been able to go to class regularly and eat and drink adequately. This morning, he awoke with a terrible headache and pain whenever he moved his neck. He has no significant medical history and takes no medications. He cannot remember the last time he received a vaccination. On physical examination, he is in extreme pain (10/10) with the following vital signs: temperature 102.4°F (39.1°C), heart rate 110 beats/minute, respiratory rate 18 breaths/minute, and blood pressure 130/75 mm Hg. His laboratory values are within normal limits, except for WBC 22,500 cells/mm^3 (82 polymorphonuclear leukocytes, 11 band neutrophils, 5 lymphocytes, and 2 monocytes). A computed tomography scan of the head is normal, so a lumbar puncture is performed with the following results: glucose 44 mg/dL (peripheral, 110), protein 220 mg/dL, and WBC 800 cells/mm^3 (85% neutrophils, 15% lymphocytes). Which is the best empiric therapy for D.M.?

   A. Penicillin G 4 million units intravenously every 4 hours.

   B. Ceftriaxone 2 g intravenously every 12 hours.

   C. Ceftriaxone 2 g intravenously every 12 hours plus dexamethasone 10 mg intravenously every 6 hours.

   D. Ceftriaxone 2 g intravenously every 12 hours plus vancomycin 1000 mg intravenously every 8 hours plus dexamethasone 10 mg intravenously every 6 hours.

F. Empiric Therapy
   1. Neonates (less than 1 month)
      a. Ampicillin plus aminoglycoside *or*
      b. Ampicillin plus cefotaxime
   2. Infants (1–23 months): Ceftriaxone plus vancomycin*
   3. Children and adults (2–50 years): Ceftriaxone plus vancomycin*
   4. Older adults (50 years and older): Ceftriaxone plus vancomycin* plus ampicillin
   5. Penetrating head trauma, neurosurgery, or CSF shunt: Vancomycin plus cefepime, ceftazidime, or meropenem

      *Vancomycin added for activity against highly drug resistant *S. pneumoniae*.

G. Therapy for Common Pathogens
   1. *S. pneumoniae*
      a. An MIC to penicillin of 0.1 mcg/mL or less
         i. Penicillin G 4 million units intravenously every 4 hours
         ii. Ampicillin 2 g intravenously every 4 hours
         iii. Alternative: Ceftriaxone 2 g intravenously every 12 hours or chloramphenicol 1–1.5 g intravenously every 6 hours
      b. An MIC to penicillin of 0.1–1.0 mcg/mL
         i. Ceftriaxone
         ii. Alternative: Cefepime 2 g intravenously every 8 hours or meropenem 2 g intravenously every 8 hours
      c. An MIC to penicillin of 2.0 mcg/mL or greater
         i. Vancomycin 15–20 mg/kg intravenously every 8–12 hours plus ceftriaxone
         ii. Alternative: Moxifloxacin 400 mg intravenously every 24 hours
         iii. If cephalosporin resistant: Vancomycin plus rifampin, vancomycin plus ceftriaxone or cefotaxime, rifampin plus ceftriaxone or cefotaxime, vancomycin plus moxifloxacin, linezolid

2. *N. meningitidis*
    a. An MIC to penicillin of less than 0.1 mcg/mL
        i. Penicillin G
        ii. Ampicillin
        iii. Alternative: Third-generation cephalosporin (cefotaxime or ceftriaxone) or chloramphenicol
    b. An MIC 0.1–1.0 mcg/mL
        i. Ceftriaxone
        ii. Alternative: Chloramphenicol, fluoroquinolone, or meropenem
3. *H. influenzae*
    a. β-Lactamase negative
        i. Ampicillin
        ii. Alternative: Third-generation cephalosporin (cefotaxime or ceftriaxone), cefepime, chloramphenicol, or fluoroquinolone
    b. β-Lactamase positive
        i. Third-generation cephalosporin (cefotaxime or ceftriaxone)
        ii. Alternative: Cefepime, chloramphenicol, or fluoroquinolone
4. *Streptococcus agalactiae*
    a. Penicillin G
    b. Ampicillin
    c. Alternative: Third-generation cephalosporin (cefotaxime or ceftriaxone)
5. *Listeria monocytogenes*
    a. Penicillin G
    b. Ampicillin
    c. Alternative: Trimethoprim/sulfamethoxazole 5 mg/kg intravenously every 6–12 hours or meropenem

H. Therapy Length: Based on clinical experience, not on clinical data
1. *N. meningitidis:* 7 days
2. *H. influenzae:* 7 days
3. *S. pneumoniae:* 10–14 days
4. *S. agalactiae*: 14–21 days
5. *Listeria monocytogenes*: 21 days or more

I. Adjunctive Corticosteroid Therapy
1. Risks and benefits
    a. Significantly less hearing loss and other neurologic sequelae in children receiving dexamethasone for *H. influenzae* meningitis
    b. Significantly improved outcomes, including decreased mortality, in adults receiving dexamethasone for *S. pneumoniae* meningitis
    c. May decrease antibiotic penetration (decreased penetration of vancomycin in animals after dexamethasone)
2. Dosage and administration
    a. Give corticosteroids 10–20 minutes before or at same time as first dose of antibiotics.
    b. Dexamethasone 0.15 mg/kg or 10 mg every 6 hours for 2–4 days
    c. Use in children with *H. influenzae* meningitis or in adults with pneumococcal meningitis; however, may need to initiate before knowing specific causative bacteria.

Patient Case

8. D.M.'s CSF cultures grew *N. meningitidis,* and now there is concern about prophylaxis. Which is the best recommendation for meningitis prophylaxis?

   A. The health care providers in close contact with D.M. should receive rifampin 600 mg orally every 12 hours for four doses.

   B. Everyone in D.M.'s dormitory and in all of his classes should receive rifampin 600 mg orally every 24 hours for 4 days.

   C. Everyone in the emergency department at the time of D.M.'s presentation should receive the meningococcal conjugate vaccine.

   D. Everyone in the emergency department at the time of D.M.'s presentation should receive rifampin 600 mg orally every 12 hours for four doses.

J. Chemoprophylaxis
   1. *N. meningitidis*
      For close contacts (household or day care) and exposure to oral secretions of index case
      a. Rifampin
         i. Adults: 600 mg every 12 hours, four doses
         ii. Children: 10 mg/kg every 12 hours, four doses
         iii. Infants (younger than 1 month): 5 mg/kg every 12 hours, four doses
      b. Ciprofloxacin 500 mg orally, one dose (adults only)
      c. Ceftriaxone 125–250 mg intramuscularly, one dose
   2. *H. influenzae*
      For all close contacts in households with unvaccinated or immunocompromised children
      a. Adults: Rifampin 600 mg daily for 4 days
      b. Children (1 month to 12 years): Rifampin 20 mg/kg/day for 4 days
      c. Infants younger than 1 month: Rifampin 10 mg/kg/day for 4 days

K. Brain Abscess
   1. Pathophysiology
      a. Direct extension or retrograde septic phlebitis from otitis media, mastoiditis, sinusitis, and facial cellulitis
      b. Hematogenous: Particularly lung abscess or infective endocarditis: 3%–20% have no detectable focus.
   2. Signs and symptoms
      a. Expanding intracranial mass lesion: Focal neurologic deficits
      b. Headache
      c. Fever
      d. Seizures
      e. Mortality is about 50%.
   3. Microbiology
      a. Usually polymicrobial
      b. *Streptococcus* spp. in 50%–60%
      c. Anaerobes in about 40%

4. Therapy
    a. Incision and drainage: By craniotomy or stereotaxic needle aspiration
    b. Suggested empiric regimens based on source of infection
        i. Otitis media or mastoiditis: Metronidazole plus third-generation cephalosporin
        ii. Sinusitis: Metronidazole plus third-generation cephalosporin
        iii. Dental sepsis: Penicillin plus metronidazole
        iv. Trauma or neurosurgery: Vancomycin plus third-generation cephalosporin
        v. Lung abscess, empyema: Penicillin plus metronidazole plus sulfonamide
        vi. Unknown: Vancomycin plus metronidazole plus third-generation cephalosporin
    c. Corticosteroids if elevated intracranial pressure

Patient Case

9. T.S. is a 48-year-old man who presents to the emergency department with fever, chills, nausea and vomiting, anorexia, lymphangitis in his right hand, and lower back pain. He has no significant medical history except for kidney stones 4 years ago. He has no known drug allergies. He is homeless and was a person with substance use disorder (intravenous heroin) for the past year but quit 2 weeks ago. On physical examination, he is alert and oriented, with the following vital signs: temperature 100.8°F (38°C), heart rate 114 beats/minute, respiratory rate 12 breaths/minute, and blood pressure 127/78 mm Hg. He has a faint systolic ejection murmur, and his right hand is erythematous and swollen. His laboratory values are all within normal limits. He had an HIV test 1 year ago, which was negative. One blood culture was obtained in the emergency department that later grew MSSA. Two more cultures were obtained 24 hours after the first culture and are now both growing gram-positive cocci in clusters. A transesophageal echocardiogram reveals vegetation on the mitral valve. Which is the best therapeutic regimen for T.S.?

    A. Nafcillin therapy for 7–10 days.

    B. Nafcillin plus rifampin plus gentamicin therapy for 6 weeks or longer.

    C. Nafcillin plus gentamicin therapy for 2 weeks of both antibiotics.

    D. Nafcillin therapy for 6 weeks.

VII. ENDOCARDITIS

A. Introduction
    1. Infection of the heart valves or other endocardial tissue
    2. Platelet-fibrin complex becomes infected with microorganisms: Vegetation
    3. Main risk factors include mitral valve prolapse, prosthetic valves, and persons who inject drugs.
    4. Three or four cases per 100,000 people per year

B. Presentation and Clinical Findings
    1. Signs and symptoms
        a. Fever: Low grade and remittent
        b. Cutaneous manifestations (50% of patients): Petechiae (including conjunctival), Janeway lesions, splinter hemorrhage
        c. Cardiac murmur (90% of patients)
        d. Arthralgias, myalgias, low back pain, arthritis
        e. Fatigue, anorexia, weight loss, night sweats

2. Laboratory findings
   a. Anemia: Normochromic, normocytic
   b. Leukocytosis
   c. Elevated erythrocyte sedimentation rate and C-reactive protein
   d. Positive blood culture in 78%–95% of patients
3. Complications
   a. Congestive heart failure: 38%–60% of patients
   b. Emboli: 22%–43% of patients
   c. Mycotic aneurysm: 5%–10% of patients

C. Microbiology (Table 12)
1. Three to five blood cultures of at least 10 mL each should be obtained during the first 24–48 hours.
2. Empiric therapy should be initiated only in acutely ill patients. In these patients, three blood samples should be obtained during a 15- to 20-minute period before antibiotics are initiated.

Table 12. Incidence of Microorganisms in Endocarditis

Organism	Incidence (%)
Streptococcus	50
Staphylococcus aureus	25
Enterococcus	8
Coagulase-negative *Staphylococcus*	7
Gram-negative bacilli	6
Candida albicans	2

D. Treatment (Table 13)

Table 13. Treatment Recommendation for Endocarditis

Organism	Recommended Therapy	Length of Therapy (wk)	
		Native Valve	Prosthetic Valve
Viridans streptococci (with PCN MIC ≤ 0.12 mcg/mL)	PCN G	4	6
	PCN G + gentamicin[a]	2	6[b]
	Ceftriaxone	4	6
	Ceftriaxone + gentamicin	2	6[b]
	Vancomycin (only if unable to tolerate PCN or ceftriaxone)	4	6
Viridans streptococci (with PCN MIC > 0.12 mcg/mL)	PCN G + gentamicin	4[c]	6[d]
	Ceftriaxone (+ gentamicin if PCN MIC > 0.5 mcg/mL)	4	6[d]
	Vancomycin (only if unable to tolerate PCN or ceftriaxone)	4	6
Staphylococcus, methicillin sensitive	Oxacillin or nafcillin Plus gentamicin and rifampin in prosthetic valves	6	≥ 6[c]
	Cefazolin (only for nonanaphylactic penicillin allergy) Plus gentamicin and rifampin in prosthetic valves	6	≥ 6[c]
	Vancomycin (only if severe PCN allergy) Plus gentamicin and rifampin in prosthetic valves	6	≥ 6[c]

Table 13. Treatment Recommendation for Endocarditis *(Cont"d)*

Organism	Recommended Therapy	Length of Therapy (wk)	
		Native Valve	Prosthetic Valve
Staphylococcus, methicillin resistant	Vancomycin Plus rifampin and gentamicin in prosthetic valves	6	≥ 6[c]
	Daptomycin (not for prosthetic valves)	6	—
Enterococcus	PCN G or ampicillin + gentamicin	4–6	6
	Vancomycin + gentamicin (only if unable to tolerate a β-lactam)	6	6
	Ampicillin + ceftriaxone	6	6
Enterococcus, PCN resistant	Vancomycin + gentamicin	6	6
Enterococcus, PCN, aminoglycoside, and vancomycin resistant	Linezolid	> 6	> 6
	Daptomycin	> 6	> 6
HACEK group	Ceftriaxone	4	6
	Ampicillin/sulbactam	4	6
	Fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin)	4	6

[a]Gentamicin should preferably be given as a single daily dose (3 mg/kg) for viridans streptococci endocarditis but may be given daily in three equally divided doses as an alternative.

[b]Gentamicin can be added for 2 wk if CrCl is greater than 30 mL/minute/1.73 m^2.

[c]Gentamicin for 2 wk.

[d]Gentamicin for 6 wk.

HACEK = *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*; MIC = minimum inhibitory concentration; PCN = penicillin.

E. Prophylaxis (Table 14)

Table 14. Endocarditis Prophylaxis

Conditions in Which Prophylaxis Is Necessary	Dental Procedures That Require Prophylaxis
Prosthetic cardiac valves including bioprosthetic and homograft valves	Any dental procedure that involves the gingival tissues or periapical region of a tooth and for procedures that perforate the oral mucosa
Previous bacterial endocarditis	
Congenital heart disease	
Unrepaired cyanotic congenital heart disease	**Other Procedures That Require Prophylaxis**
Completely repaired congenital heart defect with prosthetic material or device, during the first 6 months after the procedure	Respiratory tract
Repaired congenital heart disease with residual defects adjacent to or at the site of a prosthetic patch or device	Tonsillectomy or adenoidectomy Surgical operations that involve an incision or biopsy of the respiratory mucosa
Cardiac transplant recipients who develop cardiac valvulopathy	

F. Recommended Prophylaxis for Dental or Respiratory Tract Procedures (Table 15)

Table 15. Prophylaxis for Dental or Respiratory Tract Procedures

Situation	Agent	Regimen
Standard general prophylaxis	Amoxicillin	Adults: 2 g; children: 50 mg/kg 1 hr before procedure
Unable to take oral medications	Ampicillin	Adults: 2 g IM/IV; children: 50 mg/kg IM/IV within 30 min before procedure
	Cefazolin or ceftriaxone	Adults: 1 g IM/IV; children: 50 mg/kg IM/IV within 30 minutes before procedure
Allergic to penicillin	Clindamycin	Adults: 600 mg; children: 20 mg/kg 1 hr before procedure
	Cephalexin	Adults: 2 g; children: 50 mg/kg 1 hr before procedure
	Azithromycin or clarithromycin	Adults: 500 mg; children: 15 mg/kg 1 hr before procedure
Allergic to penicillin and unable to take oral medications	Clindamycin	Adults: 600 mg; children: 20 mg/kg IV within 30 min before procedure
	Cefazolin or ceftriaxone	Adults: 1 g IM/IV; children: 50 mg/kg IM/IV within 30 min before procedure

IM = intramuscularly; IV = intravenously.

Patient Case

10. Six months after treatment of his endocarditis, T.S. is visiting his dentist for a tooth extraction. Which antibiotic is best for prophylaxis?
    A. Tooth extractions do not warrant endocarditis prophylaxis.
    B. Administer amoxicillin 2 g 1 hour before the extraction.
    C. Administer amoxicillin 3 g 1 hour before the extraction and 1.5 g 6 hours for four doses after the extraction.
    D. T.S. is not at increased risk of endocarditis and does not need prophylactic antibiotics.

VIII. PERITONITIS AND INTRA-ABDOMINAL INFECTIONS

A. Introduction
   1. Definition: Inflammation of the peritoneum (serous membrane lining the abdominal cavity)
   2. Types
      a. Primary: Spontaneous or idiopathic, no primary focus of infection
      b. Secondary: Occurs secondary to an abdominal process

B. Primary Peritonitis: Spontaneous Bacterial Peritonitis (see the "Gastrointestinal Disorders" chapter)

C. Secondary Peritonitis
   1. Etiology:
      a. Peptic ulcer perforation
      b. Perforation of a GI organ
      c. Appendicitis
      d. Endometritis secondary to intrauterine device
      e. Bile peritonitis

f. Pancreatitis
g. Operative contamination
h. Diverticulitis
i. Intestinal neoplasms
j. Secondary to peritoneal dialysis

2. Microbiology of intra-abdominal infections
   a. Stomach and proximal small intestine: Aerobic and facultative gram-positive and gram-negative organisms
   b. Ileum: *E. coli, Enterococcus,* anaerobes
   c. Large intestine: Obligate anaerobes (i.e., *Bacteroides, Clostridium perfringens*), aerobic and facultative gram-positive and gram-negative organisms (i.e., *E. coli, Streptococcus, Enterococcus, Klebsiella, Proteus, Enterobacter*)
3. Clinical manifestations and diagnosis
   a. Fever, tachycardia
   b. Elevated WBC
   c. Abdominal pain aggravated by motion, rebound tenderness
   d. Bowel paralysis
   e. Pain with breathing
   f. Decreased renal perfusion
   g. Ascitic fluid
      i. Protein: High (more than 3 g/dL); exudate fluid
      ii. WBCs: Many, primarily granulocytes

D. Therapy: Secondary Peritonitis
1. Therapy or prophylaxis should be limited in
   a. Bowel injuries caused by trauma that are repaired within 12 hours (treat for less than 24 hours)
   b. Intraoperative contamination by enteric contents (treat for less than 24 hours)
   c. Perforations of the stomach, duodenum, and proximal jejunum (unless patient is on antacid therapy or has malignancy) (prophylactic antibiotics for less than 24 hours)
   d. Acute appendicitis without evidence of perforation, abscess, or peritonitis (treat for less than 24 hours)
2. Mild to moderate community-acquired infection
   a. Cefoxitin
   b. Cefazolin, cefuroxime, ceftriaxone, or cefotaxime plus metronidazole
   c. Ertapenem
   d. Moxifloxacin
   e. Ciprofloxacin or levofloxacin plus metronidazole
   f. Tigecycline
3. High-risk or severe* community-acquired or health care–acquired infection (*High-risk or severe is defined as APACHE II score greater than 15, advanced age, poor nutritional status/low albumin concentration, comorbidities and organ dysfunction, an inability to achieve adequate source control, presence of malignancy, severe physiologic disturbance, or immunosuppression.)
   a. Piperacillin/tazobactam
   b. Ceftazidime plus metronidazole or cefepime plus metronidazole
   c. Imipenem/cilastatin or meropenem
   d. Ciprofloxacin plus metronidazole or levofloxacin plus metronidazole (not for health care–acquired infections)
   e. Consider adding an aminoglycoside when extended-spectrum β-lactamase–producing Enterobacteriaceae or *P. aeruginosa* is of concern (health care–acquired infections only)
   f. Consider adding vancomycin for MRSA (health care–acquired infections only)

g. Add antifungal therapy if *Candida* spp. grown from intra-abdominal cultures
h. Consider using antibiotics effective against *Enterococcus* (especially if patient has received cephalosporins, has valvular disease, is immunocompromised or post-operative)

4. Therapy duration: 4 days (when source control is complete)

IX. *CLOSTRIDIOIDES DIFFICILE* INFECTION

Patient Case

11. R.K. is a 72-year-old man who presents to the emergency department with a 2-day history of redness and swelling of his upper right extremity. He scraped his arm while clearing some brush in his yard. Although the scratch was initially healing, the area around the injury has become red and warm to the touch over the past few days, and the redness appears to be spreading. His medical history includes gastroesophageal reflux disease, hypertension, hyperlipidemia, and osteoarthritis. R.K. is taking pantoprazole 40 mg orally daily, lisinopril 20 mg orally daily, atorvastatin 40 mg orally daily, and acetaminophen 500 mg orally as needed. R.K. has no known drug allergies. R.K. is hospitalized and sent home after a few days with a prescription for oral clindamycin for his cellulitis. Two weeks after completing therapy for his cellulitis, R.K. has watery diarrhea. R.K. goes to the emergency department, and his *C. difficile* toxin is positive. His WBC is 24,500 cells/mm^3, albumin is 2.8 g/dL, and SCr is 1.74 mg/dL (normally around 0.90 mg/dL). Which is the best therapeutic regimen for R.K.?

A. Metronidazole 500 mg orally three times daily for 7 days.
B. Vancomycin 125 mg orally four times daily for 10 days.
C. Fidaxomicin 200 mg orally twice daily for 14 days.
D. Rifaximin 400 mg orally twice daily for 7 days.

A. Introduction
1. *Clostridioides difficile* is transmitted by the fecal-oral route.
2. Overgrowth in the GI tract occurs after antibiotic therapy.
3. Risk factors: Hospital stays, medical comorbidities (e.g., oncology, inflammatory bowel disease, chronic kidney disease, organ transplant), extremes of age, immunodeficiency states, use of broad-spectrum antibiotics, use of proton pump inhibitors
4. Production of endotoxins A and B causes pathogenesis.
5. Symptoms: Watery diarrhea, abdominal pain, leukocytosis, GI tract complications
6. Disease severity:
a. Non-severe: Leukocytosis with WBC 15 x 10^3 cells/mm^3 or less and SCr less than 1.5 mg/dL
b. Severe: Leukocytosis with WBC 15 x 10^3 cells/mm^3 or greater or SCr greater than 1.5 mg/dL
c. Fulminant: Hypotension or shock, ileus, megacolon
7. BI/NAP1 strain produces more enterotoxin, produces binary toxin, has increased sporulation capacity, and is resistant to fluoroquinolones. Increased risk of metronidazole failure, morbidity, and mortality

B. Therapy
1. Initial episode
a. Nonsevere infection
i. Vancomycin 125 mg orally four times a day for 10 days
ii. Fidaxomicin 200 mg orally twice daily for 10 days. No difference in clinical cure rates compared with vancomycin but lowered incidence of recurrence
iii. Metronidazole may be used if the above two agents are not available (500 mg orally three times daily for 10 days)

b. Severe infection
    i. Vancomycin 125 mg orally four times a day for 10 days
    ii. Fidaxomicin 200 mg orally twice daily for 10 days
c. Fulminant infection: Vancomycin 500 mg orally four times a day plus metronidazole 500 mg intravenously every 8 hours (if complete ileus, add vancomycin per rectum 500 mg in 100-500 mL of saline as an enema four times a day)

2. First recurrence
    a. Following metronidazole: Vancomycin 125 mg orally four times daily for 10 days
    b. Following vancomycin:
        i. Vancomycin prolonged taper and pulsed dosing: 125 mg orally four times daily for 10-14 days, then twice daily for a week, then daily for a week then every 2-3 days for 2-8 weeks
        ii. Fidaxomicin 200 mg orally two times daily for 10 days
    c. Following fidaxomicin: Vancomycin prolonged taper and pulsed dosing
3. Second and subsequent recurrences
    a. Vancomycin prolonged taper and pulsed dosing
    b. Vancomycin 125 mg orally four times daily for 10 days followed by rifaximin 400 mg three times daily for 20 days
    c. Fidaxomicin 200 mg orally twice daily for 10 days
    d. Fecal microbiota transplantation
4. Recurrence prevention with bezlotoxumab
    a. Human monoclonal antibody that binds to *C. difficile* toxin B preventing recurrent infections.
    b. Indicated in patients who are at high risk of recurrence (older than 65, one or more prior episodes within the previous 6 months, immunocompromised, clinically severe CDI at presentation, or virulent strain [ribotype 027, 078 or 244]).
    c. Dose: 10 mg/kg intravenously as a single 60-minute infusion given during standard antibiotic therapy (does *not* replace standard antibiotic therapy)
    d. Lower incidence of recurrent *C. difficile* infection in 12 weeks (17% versus 27%).

Patient Case

12. You are a pharmacist who works closely with the surgery department to optimize therapy for patients undergoing surgical procedures at your institution. The surgeons provide you with principles of surgical prophylaxis that they believe are appropriate. Which is the best practice for optimizing surgical prophylaxis?

    A. Antibiotics should be redosed for extended surgical procedures; redose if the surgery lasts longer than 4 hours or involves considerable blood loss.

    B. All patients should be given antibiotics for 24 hours after the procedure; this will optimize prophylaxis.

    C. Preoperative antibiotics can be given up to 4 hours before the incision; this will make giving the antibiotics logistically easier.

    D. Vancomycin is the antibiotic of choice for surgical wound prophylaxis because of its long half-life and activity against MRSA.

X. SURGICAL PROPHYLAXIS

A. Introduction
    1. Prophylaxis: Administering the putative agent before bacterial contamination occurs
    2. Early therapy: Immediate or prompt institution of therapy as soon as the patient presents; usually, contamination or infection will have preceded the initiation of therapy (e.g., dirty wounds).

B. Classification of Surgical Procedures (Table 16)

Table 16. Classification of Surgical Procedures

Surgical Procedure	Infection Rate (%)
Clean: No entry is made in the respiratory, GI, or genitourinary tracts or in the oropharyngeal cavity In general, it is elective with no break in technique and no inflammation encountered	1–4
Clean contaminated: Entry in the respiratory, GI, genitourinary, or biliary tracts or oropharyngeal cavity without unusual contamination Includes clean procedures with a minor break in technique	5–15
Contaminated: Includes fresh traumatic wounds, gross spillage from the GI tract (without a mechanical bowel preparation), a major break in technique, or incisions encountering acute, nonpurulent inflammation	16–25
Dirty: Includes procedures involving old traumatic wounds, perforated viscera, or clinically evident infection	30–100

C. Risk Factors for Postoperative Wound Infections
   1. Bacterial contamination
      a. Exogenous sources: Flaw in aseptic technique
      b. Endogenous sources
         i. Most important except in clean procedures
         ii. Patient flora causes infection
   2. Host resistance
      a. Extremes of age
      b. Nutrition (i.e., malnourished patients)
      c. Obesity
      d. Diabetes mellitus (decreased wound healing and increased risk of infection)
      e. Immunocompromised
      f. Hypoxemia
      g. Remote infection
      h. Presence of foreign body (healthy person tolerates inoculum of 10^5, but in the presence of a foreign body, only 10^2 are needed)

D. Indications for Surgical Prophylaxis
   1. Common postoperative infection with low morbidity
   2. Uncommon postoperative infection with significant morbidity and mortality

E. Principles of Prophylaxis (Figure 1)
   1. Timing: Antibiotics must be present in the tissues at the time of bacterial contamination (incision) and throughout the operative period; on-call dosing is not acceptable.
      a. Administering antibiotics earlier than immediately preoperatively (within 60 minutes before incision or 60–120 minutes if using vancomycin or a fluoroquinolone) is unnecessary.
      b. Initiating antibiotics postoperatively is no more effective than administering no prophylaxis.
      c. Antibiotics should be redosed for extended surgical procedures.
      d. Redose if the surgery lasts longer than 4 hours (or more than 2 half-lives of the antibiotic) or involves considerable blood loss.

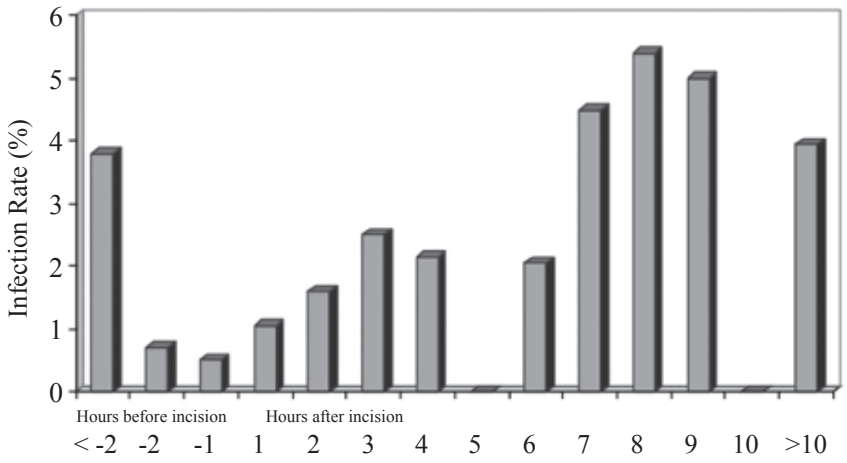

Figure 1. Principles of prophylaxis.

Source: Information from: Classen DC, Evans RS, Pestotnik SL, et al. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. N Engl J Med 1992;326:281-6.

2. Dosage
    a. Adequate dosing is necessary to prevent postoperative skin infections. Obese patients have a higher incidence of postoperative infections.
    b. Appropriate dosing
        i. Cefazolin: 2 g (3 g for patients weighing 120 kg or more)
        ii. Ceftriaxone, cefotetan, cefoxitin: 2 g
        iii. Clindamycin: 900 mg
        iv. Vancomycin: 15 mg/kg
3. Duration
    a. Most procedures, including GI, orthopedic, and gynecologic procedures, warrant antibiotics only as long as the patient is in the operating room; administration beyond surgical closure is not necessary.
    b. Cardiac procedures may warrant 24 hours of antibiotics after surgery.
4. Spectrum
    a. Need only activity against skin flora unless the operation violates a hollow viscus mucosa
    b. GI, genitourinary, hepatobiliary, and some pulmonary operations warrant additional antibiotics.
    c. Colorectal surgery is one procedure in which broad-spectrum aerobic and anaerobic coverage is most effective.
    d. Try to avoid a drug that may be needed for therapy if infection occurs.
5. Adverse reactions and bacterial resistance
    a. Antibiotic prophylaxis should not cause greater morbidity than the infection it prevents.
    b. Overuse may lead to resistance, which could prevent further use of the antibiotic for surgical prophylaxis or other infections (duration of administration is an important factor).
6. Cost
    a. Prophylaxis can account for a substantial portion of the antibiotic budget.
    b. Must be weighed against the cost of treating one person with a postoperative infection

F. Antibiotic Prophylaxis in Specific Surgical Procedures
Note: For patients colonized with MRSA, a single preoperative dose of vancomycin can be added.
1. GI
   a. Gastric or duodenal
      i. Because of acidity, little normal flora
      ii. Rates of intragastric organisms and postoperative infections increase with increasing pH.
      iii. Indicated for morbid obesity, esophageal obstruction, decreased gastric acidity, or decreased GI motility
      iv. Recommendation: Cefazolin 2 g before induction
   b. Biliary
      i. Biliary tract normally has no organisms.
      ii. Indicated for high-risk patients. (Often, intraoperative cholangiography reveals unexpected common duct stones, so some studies recommend using antibiotics in all biliary surgery. In addition, studies have shown an increase in infection rates without risk factors.)
         (a) Acute cholecystitis
         (b) Obstructive jaundice
         (c) Common duct stones
         (d) Age older than 70 years
      iii. Recommendation: Cefazolin, cefoxitin, cefotetan, or ceftriaxone 2 g or ampicillin/sulbactam 3 g before induction
   c. Appendectomy
      i. Acutely inflamed or normal appendix: Less than 10% risk
      ii. Evidence of perforation: More than 50% risk (treatment necessary)
      iii. If perforated appendix, treat for 3–7 days.
      iv. Recommendation: Cefoxitin or cefotetan 2 g (or cefazolin plus metronidazole) before induction
   d. Colorectal
      i. A 30%–77% infection rate without antibiotics
      ii. One of the few surgical procedures in which coverage for aerobes *and* anaerobes has proved most effective
      iii. Preoperative antibiotics
         (a) Combined oral and parenteral regimens may be better than parenteral regimens alone.
         (b) Oral regimens are inexpensive; however, some data suggest they are less effective when used alone (without parenteral agents), have greater toxicity, and may increase the risk of *C. difficile* infections.
   e. Recommendation
      i. Cefazolin or ceftriaxone 2 g plus metronidazole 500 mg (or cefoxitin or cefotetan 2 g or ampicillin/sulbactam 3 g or ertapenem 1 g or gentamicin/tobramycin 5 mg/kg plus clindamycin 900 mg–metronidazole 500 mg) before induction
      ii. With or without neomycin 1 g orally and erythromycin 1 g orally at 19, 18, and 9 hours before surgery or neomycin 2 g orally and metronidazole 2 g orally at 13 and 9 hours before surgery
      iii. Mechanical bowel preparation is not recommended and may be harmful.
2. Obstetrics and gynecology
   a. Vaginal or abdominal hysterectomy
      i. Antibiotics are most effective in vaginal hysterectomies but generally are given for both procedures.
      ii. Recommendation: Cefazolin or cefoxitin or cefotetan 2 g (or ampicillin/sulbactam 3 g) before induction
   b. Cesarean section. Recommendation: Cefazolin 2 g after the cord is clamped

3. Cardiothoracic
    a. Cardiac surgery
        i. Antibiotics decrease the risk of mediastinitis.
        ii. Recommendation: Cefazolin or cefuroxime 2 g preinduction (plus intraoperative doses), if MRSA is probable or patient has been hospitalized, use vancomycin
    b. Pulmonary resection (i.e., lobectomy and pneumonectomy). Recommendation: Cefazolin 2 g before induction (or ampicillin/sulbactam 3 g or vancomycin 15 mg/kg)
    c. Vascular surgery
        i. High mortality with infected grafts
        ii. Recommendation: Cefazolin 2 g before induction and every 8 hours for three doses; if MRSA is probable, use vancomycin
4. Orthopedic
    a. Prophylaxis is indicated when surgery involves prosthetic materials (i.e., total hip or knee, nail, or plate).
    b. Recommendation: Cefazolin 2 g before induction (or vancomycin)
5. Head and neck
    a. Indicated for major surgical procedures when an incision is made through the oral or pharyngeal mucosa
    b. Recommendation: Cefazolin or cefuroxime 2 g plus metronidazole 500 mg or ampicillin/sulbactam 3 g or clindamycin 900 mg before induction
6. Urologic
    a. In general, not recommended
    b. Indicated if patient has a positive urine culture before surgery (should treat and then operate)
    c. If therapy is unsuccessful, cover for the infecting organism and operate.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C

Although ampicillin/sulbactam has good activity against *H. influenzae*, *Moraxella catarrhalis*, and *S. pneumoniae* (but not drug-resistant *S. pneumoniae* [DRSP]), it has no activity against atypical organisms (*L. pneumophila*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*). Current recommendations are to include a macrolide with a β-lactam antibiotic for hospitalized patients with CAP (Answer A is incorrect). Piperacillin/tazobactam has good activity against *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae* (but not DRSP) and, with gentamicin, is excellent for pneumonia caused by most gram-negative organisms. However, this increased activity is not necessary for CAP, and the combination has no activity against atypical organisms (Answer B is incorrect). Ceftriaxone plus azithromycin is the best initial choice. It has excellent activity against atypical organisms (because of azithromycin), *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae* (even intermediate DRSP) (Answer C is correct). Although doxycycline has activity against atypical organisms and most of the typical organisms that cause CAP, it is not recommended as monotherapy in hospitalized patients. In addition, its activity against *S. pneumoniae* may be limited (if the patient lives in an area with extensive DRSP). Doxycycline would not be the best initial choice (Answer D is incorrect).

2. Answer: D

Ceftriaxone plus gentamicin plus linezolid is not good empiric therapy because ceftriaxone has no activity against *P. aeruginosa*. Because the patient has been in a hospital for 5 days or more (8 days at this point), she is at increased risk of MDR organisms, specifically *P. aeruginosa* and MRSA (Answer A is incorrect). Although piperacillin/tazobactam has good activity against most common causes of nosocomial pneumonia (including *P. aeruginosa*), the most recent guidelines recommend two antibiotics with activity against *P. aeruginosa* for patients with risk factors for MDR organisms She also needs an antibiotic with MRSA activity (Answer B is incorrect). Levofloxacin has activity against *P. aeruginosa,* but two drugs should be used (Answer C is incorrect). Cefepime plus tobramycin plus vancomycin is the best empiric therapy because it includes two antibiotics with activity against *P. aeruginosa* and another agent for MRSA (Answer D is correct).

3. Answer: C

This patient has symptoms suggestive of bacterial sinusitis, including two major symptoms and a few minor symptoms. That the symptoms improved and then worsened suggests a bacterial sinusitis that followed a viral infection (Answer D is incorrect). Although the combination of cefpodoxime and clindamycin is an option for sinusitis in penicillin-allergic patients, it is not recommended to give either of these alone for treatment (Answers A and B are incorrect). The best option is amoxicillin/clavulanate, which has activity against organisms commonly seen in bacterial sinusitis and is considered a first-line agent (Answer C is correct).

4. Answer: B

Although the treatment duration is correct for this patient's diagnosis (7 days), oral trimethoprim/sulfamethoxazole is inappropriate for complicated pyelonephritis. It will also interact with warfarin, increasing the risk of bleeding. (Answer A is incorrect). Ciprofloxacin 400 mg intravenously twice daily and then 500 mg orally twice daily for 7 days is an appropriate choice and duration (7–14 days) for this complicated pyelonephritis (it may also interact with warfarin but to a lesser extent than trimethoprim/sulfamethoxazole). It would be expected to have activity against the common organisms causing complicated pyelonephritis (Answer B is correct). Gentamicin for 3 days is too short a treatment duration (Answer C is incorrect). Tigecycline, followed by doxycycline, is not recommended for complicated pyelonephritis (although tigecycline is found unchanged in the urine) (Answer D is incorrect).

5. Answer: C

Nafcillin has excellent activity against gram-positive organisms, but it would miss the gram-negative organisms and anaerobes often involved in moderate to severe diabetic foot infections (Answer A is incorrect). Tobramycin and levofloxacin would be good against aerobic organisms, but levofloxacin has only limited activity against anaerobes. Tobramycin may also not be a good choice for a patient with diabetes mellitus with long-term complications (because of the increased risk of nephrotoxicity) (Answer B is incorrect). β-Lactamase inhibitor combinations are good agents because they have activity against the organisms that are often involved. At this time, a regimen active

against *P. aeruginosa* is probably not necessary. Treatment duration may need to be extended if the bone is involved (Answer C is correct). Aggressive antibiotic treatment often prevents the need for an amputation (Answer D is incorrect).

6. Answer: A
Because sensitivities of the gram-positive organism are still unknown, vancomycin is the best choice. In addition, the therapy duration for osteomyelitis is 4–6 weeks (Answer A is correct). Therefore, the 2-week duration with nafcillin is too short (Answer B is incorrect). Although levofloxacin is advantageous because it can be given orally, it will probably not achieve adequate bone concentrations to eradicate *S. aureus* (the most likely organism) (Answer C is incorrect). Ampicillin/sulbactam is effective against *S. aureus* (except for MRSA); its broad spectrum of activity is not necessary in this situation, and the duration is too short (Answer D is incorrect).

7. Answer: D
From his presentation and laboratory values, this patient has bacterial meningitis. The gram-negative cocci on Gram stain are probably *N. meningitidis*. Penicillin is effective against *N. meningitidis;* however, some strains are resistant, and until culture results are received, it is unwise to use this agent alone (Answer A is incorrect). Ceftriaxone is the appropriate empiric antibiotic therapy in this situation; however, vancomycin is generally added empirically because of its activity against highly penicillin-resistant *S. pneumoniae* (Answer B and C is incorrect). Dexamethasone is primarily beneficial in adults with pneumococcal meningitis, but it should be included empirically until culture results are finalized (Answer D is correct). Vancomycin and dexamethasone can be discontinued when pneumococcal meningitis is ruled out.

8. Answer: A
Only people in close contact to a patient with meningococcal meningitis need prophylaxis (primarily those who live closely with the patient and those who are exposed to oral secretions) (Answer B and D are incorrect). The correct regimen is rifampin 600 mg every 12 hours for four doses (Answer A is correct). Although the vaccine is a good idea for those at future risk of acquiring this infection (e.g., college students living in dormitories), its use during an outbreak is very limited (Answer C is incorrect).

9. Answer: D
A treatment duration of 7-10 days is too short for *S. aureus* endocarditis in the mitral position (Answer A is incorrect). Only streptococcal endocarditis can be treated for 2 weeks. Although nafcillin intravenously plus rifampin plus gentamicin therapy for 6 weeks or longer is an appropriate duration for MSSA, the rifampin and gentamicin need not be added in patients with native valve endocarditis (Answer B is incorrect). Nafcillin intravenously plus gentamicin intravenously for 2 weeks is too short for *S. aureus* endocarditis (Answer C is incorrect). Nafcillin intravenously for 6 weeks is the recommended treatment for MSSA endocarditis (Answer D is correct).

10. Answer: B
This patient is at increased risk of endocarditis because of his history of the disease (Answer D is incorrect). Tooth extractions warrant prophylaxis for those at risk (Answer A is incorrect) Amoxicillin 2 g, 1 hour before the tooth extraction, is the current recommended dose (Answer B is correct). The 2-g dose is adequate for protection, and a follow-up dose is not needed. Amoxicillin 3 g 1 hour before the extraction and 1.5 g 6 hours for four doses after the extraction is the older recommended dose. A follow-up dose is not needed (Answer C is incorrect).

11. Answer: B
This patient is having a severe episode of *C. difficile* diarrhea, as demonstrated by his low albumin, high WBC, and elevated SCr. Therefore, metronidazole is not the optimal choice (and the duration is too short) (Answer A is incorrect). Fidaxomicin and rifaximin are not first-line agents (Answers C and D are incorrect). Fidaxomicin could be used first line in patients who are at high risk of recurrence, but the duration of 14 days is too long. The best therapy for this patient is vancomycin for 10 days (Answer B is correct).

12. Answer: A
Redosing antibiotics for surgical prophylaxis is very important, especially for antibiotics with short half-lives, for extended surgical procedures, or for when there is extensive blood loss (Answer A is correct).

Antibiotics given beyond the surgical procedure are generally unnecessary and only increase the potential for adverse drug reactions and resistant bacteria (Answer B is incorrect). Although preoperative antibiotics given up to 4 hours before the incision may improve the logistics of administering surgical prophylaxis, study results show that antibiotics must be given as close to the time of the incision as possible (definitely within 2 hours) (Answer C is incorrect). Vancomycin should not be used routinely for surgical prophylaxis. The Centers for Disease Control and Prevention does not recommend the use of vancomycin for "routine surgical prophylaxis other than in a patient with life-threatening allergy to β-lactam antibiotics."(Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A

The patient has CAP that does not require hospitalization (CURB-65 score is 1 at most [no mention of mental status]). Because he has not received any antibiotics in the past 3 months and has no comorbidities, he is at low risk of DRSP. Therefore, the drug of choice is either a macrolide or doxycycline (Answer A is correct). Cefuroxime is not recommended for the treatment of CAP (Answer B is incorrect). Fluoroquinolones are recommended only if the patient has had recent antibiotics or has comorbidities (Answer C is incorrect). Trimethoprim/sulfamethoxazole is not used for CAP (Answer D is incorrect).

2. Answer: D

The symptoms of this patient (high temperature, malaise, dry cough, nasal congestion, and severe headaches) are most consistent with influenza; therefore, an antibacterial agent would not affect recovery (Answers A and B are incorrect). Oseltamivir should be initiated within 48 hours of symptom onset, so because this patient is more than 3 days out from symptom onset, oseltamivir will not affect recovery (Answer C is incorrect). Because of the viral etiology and time since symptom onset, symptomatic treatment is all that is indicated (Answer D is correct).

3. Answer: B

A case-control study would be the most appropriate study design because it is the most ethical, cost-effective, timely method (Answer B is correct). A stronger study design—for instance, a prospective cohort study or a randomized controlled trial—has many disadvantages if used to answer this question. In a prospective cohort study, too many patients would need to be observed because of the low incidence of confirmed pneumococcal pneumonia. This study would be too costly and take too long to complete (Answer C is incorrect). Randomized controlled trials also have many disadvantages in this situation. First, patients would need to be vaccinated and then observed for at least 10 years. Second, too many patients would need to be observed because of the low incidence of confirmed pneumococcal pneumonia. Third, it would be unethical to randomly assign half of the patients to no vaccination. This study would therefore be too costly, unethical, and time-consuming (Answer D is incorrect). A case series would evaluate only a few patients given a diagnosis of pneumococcal pneumonia 10 years or more after vaccination. It would not provide comparative data, nor would it provide a strong study design (Answer A is incorrect).

4. Answer: C

Although necrotizing fasciitis can be caused by *Streptococcus* only, it is often a mixed infection that includes gram-positive, gram-negative, and anaerobic bacteria. Therefore, in addition to urgent surgical debridement, it must be treated empirically with broad-spectrum antibiotics. It is recommended that one of those antibiotics have activity against *P. aeruginosa*. Clindamycin therapy is also recommended initially to decrease the production of toxin by *Streptococcus*. Because vancomycin alone has no activity against gram-negative organisms and does not decrease toxin production, it is not the best empiric agent (Answer A is incorrect). Moreover, piperacillin/tazobactam alone has no activity against MRSA and does not decrease toxin production (Answer B is incorrect). Although there are some data that azithromycin may also decrease toxin production and that linezolid has MRSA activity, ceftriaxone has no activity against *P. aeruginosa* (Answer D is incorrect). The best empiric option is vancomycin plus meropenem plus clindamycin (Answer C is correct).

5. Answer: C

Although nitrofurantoin is a recommended first-line agent, the therapy duration is too short for its use (Answer A is incorrect). Because this patient has no contraindications to the use of trimethoprim/sulfamethoxazole or nitrofurantoin, and trimethoprim/sulfamethoxazole resistance rates are not mentioned as being high, fluoroquinolones would not be considered appropriate as first-line therapy in this particular case (Answer B is incorrect). In addition, 7 days of therapy is not necessary. The best choice for this patient is trimethoprim/sulfamethoxazole double strength twice daily orally for 3 days. The patient should be counseled about the potential interaction between antibiotics and oral contraceptives (Answer C is correct). β-Lactams are not as effective as trimethoprim/sulfamethoxazole, and data are limited on their use for 3 days (Answer D is incorrect).

6. Answer: A

For the asymptomatic patient who is bedridden and chronically catheterized, with cloudy urine and bacteria revealed by urinalysis, no therapy is indicated (Answer A is correct). All patients with chronic urinary catheters will be bacteriuric. Because this patient is asymptomatic, the catheter does not need to be replaced (Answer B is incorrect). If she were symptomatic, catheter replacement might be indicated. Antibiotics are not indicated; however, a 7-day course would be appropriate if treatment were instituted (Answer C and D are incorrect). A long course of treatment only increases the risk of acquiring resistant organisms.

7. Answer: A

Because cellulitis (which the patient appears to have) is usually caused by *Streptococcus* or *Staphylococcus*, cefazolin is the drug of choice (vancomycin could be initiated empirically if MRSA were a concern in this patient) (Answer A is correct). Although penicillin is the treatment of choice for erysipelas, the patient probably has acute cellulitis (there is no raised border at the edge of the infection, which indicates erysipelas) (Answer B is incorrect). Although piperacillin/tazobactam has activity against both *Streptococcus* and *Staphylococcus,* this treatment is too broad spectrum for an acute cellulitis (Answer C is incorrect). Because Doppler studies are negative, the likelihood of a deep venous thrombosis is low (Answer D is incorrect).

8. Answer: C

Even if a patient is believed to have aseptic meningitis after analysis of the CSF, antibiotics must be given until CSF cultures are negative (Answer A is incorrect). In empiric therapy for bacterial meningitis in adults (i.e., when the CSF Gram stain is negative), ceftriaxone should be used in combination with vancomycin (Answer B is incorrect). The vancomycin is necessary for activity against resistant *S. pneumoniae (*Answer C is correct). Although the symptoms and CSF results are similar to what is expected for herpes simplex encephalitis, the use of acyclovir alone in this patient is inappropriate. Antibacterials must be used as well. Viral meningitis is generally caused by coxsackievirus, echovirus, and enterovirus, which are not treated with acyclovir (Answer D is incorrect).

9. Answer: C

Enterococcal endocarditis should be treated for 4–6 weeks. The 2-week treatment regimen is indicated only for streptococcal endocarditis *(*Answer A is incorrect). There is also no indication that the patient is penicillin allergic; thus, vancomycin should not be used as first-line treatment (Answer B is incorrect). Ampicillin plus ceftriaxone for 4–6 weeks is a regimen of choice for penicillin-susceptible enterococcal endocarditis (Answer C is correct). Cefazolin has no activity against *Enterococcus;* therefore, the regimen with cefazolin is inappropriate (Answer D is incorrect).

10. Answer: C

A perforated appendix requires antibiotics after surgery for an intra-abdominal infection (Answer D is incorrect). The combination of vancomycin and metronidazole does not have adequate activity against aerobic, gram-negative organisms (e.g., *E. coli*) (Answer A is incorrect). The combination of cefazolin and ciprofloxacin does not have adequate activity against anaerobic organisms (e.g., *B. fragilis* group) (Answer B is incorrect). Ceftriaxone plus metronidazole is a good choice for intra-abdominal infections, although it has limited activity against *Enterococcus* (Answer C is correct).

11. Answer: D

β-Lactam antibiotics are not recommended first-line agents for patients with acute bacterial prostatitis. Therefore, amoxicillin/clavulanate and cefprozil are not the best options in this patient (Answers A and C are incorrect). Although trimethoprim/sulfamethoxazole is an appropriate antibiotic, 14 days of treatment is too short for prostatitis. Treatment duration should be 4 weeks (Answer B is incorrect). Fluoroquinolones are an appropriate antibiotic class for prostatitis, and the 28-day duration is also appropriate (Answer D is correct).

12. Answer: B

Because the organism causing the infection is known to be MSSA, using vancomycin or daptomycin is unnecessary. They both can potentially cause serious toxicities, and daptomycin is expensive (Answers A and D are incorrect). Both nafcillin and cefazolin are appropriate choices for MSSA osteomyelitis; however, because this infection involves a prosthetic joint rifampin must be combined with the primary antibiotic, and

this combination must continue for 2–6 weeks (Answer C is incorrect). This must be followed with 3 months of appropriate oral antibiotics. (Answer B is correct).

13. Answer: A

For any orthopedic surgical procedures in which prosthetic materials will be implanted, surgical prophylaxis is necessary. The preferred agent is cefazolin, although vancomycin may be used in patients with allergies. The recommended dosage of cefazolin is at least 2 g (3 g for those weighing more than 120 kg) (Answers C and D are incorrect). Antibiotics must be present in the tissues at the time of incision, and it is best to administer the agent within 1 hour of the incision (Answer A is correct). Because orthopedic procedures tend to be shorter procedures, redosing is probably unnecessary. Administering antibiotics beyond surgical closure is unnecessary (Answer B is incorrect).

Infectious Diseases II

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Infectious Diseases II

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Learning Objectives

1. Formulate an appropriate regimen to prevent or treat HIV infections, including initiating and monitoring therapy.
2. Discuss appropriate treatment of the various acquired immunodeficiency syndrome opportunistic infections, including primary and secondary prophylaxis.
3. Describe appropriate treatment and preventive therapy for tuberculosis, including infections with drug-resistant organisms.
4. Design appropriate therapeutic regimens for treating systemic and superficial fungal infections and classify the various antifungal agents.

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. K.E. is a 29-year-old asymptomatic patient who is HIV positive. She recently found out she is pregnant and is estimated to be early in her first trimester. Her most recent CD4 count was 170 cells/mm^3, and her viral load was 100,000 copies/mL by reverse transcriptase polymerase chain reaction. Which is the best therapy for K.E. to prevent HIV transmission to her child?
   A. No drug therapy is needed; the risks to the fetus outweigh any benefits.
   B. Administer zidovudine 300 mg twice daily orally throughout the pregnancy, followed by zidovudine during labor and consequently to the infant for 6 weeks.
   C. No drug therapy is needed now, but administer a single dose of nevirapine at the onset of labor.
   D. Administer a potent combination antiretroviral therapy (ART) regimen.

2. R.E. is a 33-year-old man who recently tested HIV positive. He is initiated on tenofovir alafenamide, emtricitabine, and dolutegravir. Which is the best counseling for R.E.?
   A. Watch for trouble sleeping because dolutegravir can cause insomnia.
   B. If you think you are having a drug-related adverse effect, cut the dose of all of your drugs in half.
   C. Talk to your pharmacist about drug interactions because both dolutegravir and tenofovir inhibit cytochrome P450 (CYP) 3A4.
   D. Tenofovir and emtricitabine cause additive peripheral neuropathy, so let your pharmacist know if you have tingling in your extremities.

3. P.P., a 43-year-old man who is HIV positive, presents to the clinic with a headache that has gradually worsened during the past 2 weeks. He does not feel very sick and has not experienced any focal seizures. His most recent CD4 count was 35 cells/mm^3. His laboratory values are as follows: Gram stain negative, white blood cell count 2 cells/mm^3, protein 35 mg/dL, glucose 75 mg/dL (peripheral 110 mg/dL), India ink positive, and cryptococcal antigen 1:1024. He is given a diagnosis of cryptococcal meningitis and successfully treated. Which is the best follow-up therapy for P.P.?
   A. No maintenance treatment is necessary.
   B. Administer fluconazole 200 mg/day orally.
   C. Administer amphotericin B 1 mg/kg/week intravenously.
   D. He is protected as long as he is also receiving *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP, PJP) prophylaxis.

4. A study compares the incidence of active tuberculosis (TB) infection in patients receiving isoniazid versus rifampin for latent TB infection. After completing therapy (6 months for isoniazid and 4 months for rifampin), 0.3% in the isoniazid group and 0.8% in the rifampin group progress to active disease. Which best represents how many patients would need to be treated with isoniazid over rifampin to prevent one progression to active disease?
   A. 5.
   B. 50.
   C. 200.
   D. Insufficient information to calculate this number.

5. G.T. is a 34-year-old woman positive for HIV who is brought to the emergency department by her boyfriend after experiencing headaches, a change in mental status, and loss of feeling on her right side. A computed tomographic scan shows two large ring-enhancing lesions in her brain indicating toxoplasmic encephalitis. Her most recent CD4 count was 85 cells/mm^3, but that was 4 months ago. She currently takes no antiretroviral agents but does take dapsone for PCP prophylaxis. Which is the best therapy for G.T.?
   A. Atovaquone for 4–6 weeks.
   B. High-dose trimethoprim/sulfamethoxazole plus clindamycin for 6 weeks.
   C. Pyrimethamine plus sulfadiazine for 6 weeks.
   D. Pyrimethamine plus clindamycin and leucovorin for 6 weeks.

6. H.Y., a 49-year-old man with acute myeloid leukemia, is given a diagnosis of TB and initiated on empiric therapy with rifampin, isoniazid, ethambutol, and pyrazinamide. Three months into his TB therapy, he is hospitalized and given a diagnosis of aspergillosis; treatment is needed in addition to his TB treatment. Which is the best antifungal to use in H.Y.?
   A. Fluconazole.
   B. Voriconazole.
   C. Isavuconazonium.
   D. Amphotericin lipid formulation.

7. P.I. is a 35-year-old woman who presents to the clinic with a 2-week history of night sweats, fatigue, weight loss, and a persistent cough. A tuberculin skin test (TST) is placed, and a sputum sample is taken; then, P.I. is sent home with a prescription for levofloxacin 750 mg/day orally. Two days later, her TST is measured at 20-mm induration, and her sputum sample is positive for acid-fast bacilli. P.I., who has no pertinent medical history, has never been outside the United States. She lives in an area with an extremely low incidence of multidrug-resistant TB. Which regimen is the best therapy for P.I.?
   A. Isoniazid for 6 months.
   B. Isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 more months.
   C. Isoniazid and rifampin for 6 months.
   D. Levofloxacin isoniazid and rifampin for both TB and other bacterial causes of pneumonia.

8. A prospective, double-blind study compared the effects of two therapies—a potent combination ART with a ritonavir-boosted protease inhibitor (PI) and a potent combination ART with dolutegravir—in 350 patients with HIV. Which is the best statistical test to use to compare end points such as the mean change in viral load or mean change in CD4 counts?
   A. Analysis of variance.
   B. Chi-square test.
   C. Student t-test.
   D. Wilcoxon rank sum test.

9. J.Z. is a 42-year-old HIV-positive man with a diagnosis of cytomegalovirus (CMV) retinitis 9 months ago. Since then, he has been treated with valganciclovir. When he received a diagnosis of CMV retinitis, his CD4 count was 17 cells/mm^3, and he was initiated on combination ART. Three months ago, his CD4 count was 175 cells/mm^3. Today, his CD4 count is 312 cells/mm^3. Which is the best recommendation for valganciclovir therapy in J.Z.?
   A. Discontinue valganciclovir because his CD4 count has been above 100 cells/mm^3 for 3 months.
   B. Continue valganciclovir until the CD4 count has been above 100 cells/mm^3 for 1 year.
   C. Finish 1 year of therapy with valganciclovir and then discontinue the medication if his CD4 count is still above 100 cells/mm^3.
   D. Continue valganciclovir indefinitely.

10. K.T. is a 55-year-old woman who is hospitalized with a presumed *Candida* infection. She currently receives simvastatin, diazepam, lisinopril, dofetilide, and metoprolol. Which azole antifungal would be best to use to avoid interactions with the other medications K.T. is receiving?
    A. Itraconazole.
    B. Fluconazole.
    C. Voriconazole.
    D. Isavuconazonium.

11. T.E. is a 51-year-old man who has been HIV positive since 1998. He is hospitalized for cellulitis and reports that he has not taken his ART for at least a year. His current CD4 count is 112 cells/mm^3. He is allergic to penicillins and sulfa antibiotics. Which regimen is the best PCP prophylaxis for T.E.?
    A. Trimethoprim/sulfamethoxazole double strength by mouth daily.
    B. Dapsone 100 mg by mouth weekly.
    C. Atovaquone 1500 mg by mouth daily.
    D. Pentamidine 300 mg by nebulization once monthly.

12. O.D. is a 38-year-old HIV positive man originally from Puerto Rico who moved to the continental United States four years ago. He is hospitalized for fever, weight loss, chills, myalgia, and lymphadenopathy. He is initially treated for PCP but his symptoms worsen. A bronchoscopy is performed and the cultures are positive for *Histoplasma capsulatum*. What is the best treatment for O.D.?
    A. Amphotericin B lipid formulation for 1-2 weeks followed by itraconazole 200 mg daily for 12 weeks total.
    B. Micafungin 100 mg IV daily for 1-2 weeks followed by fluconazole 400 mg daily for 12 weeks total.
    C. Voriconazole 200 mg twice daily for 6 weeks total.
    D. Isavuconazole 200 mg every 8 hours for 2 days followed by 200 mg daily for 6 weeks total.

13. R.V. is a 35-year-old man who presents to the emergency department with a persistent cough, night sweats, and an unintentional 15 kg recent weight loss. He has been homeless for over 3 years and has been living at multiple shelters in the city. An interferon-gamma release assay test is positive and his sputum is AFB positive. He is not HIV-infected. Which one of the following would be the best empiric therapy for R.V.?
    A. Rifampin, isoniazid, pyrazinamide, and ethambutol 3 times weekly for 2 months followed by rifampin and isoniazid 2 times weekly for 4 months.
    B. Rifampin, isoniazid, pyrazinamide, and ethambutol daily for 2 months followed by rifampin and isoniazid 5 times weekly for 4 months.
    C. Rifampin, isoniazid, pyrazinamide, and ethambutol daily for 2 months followed by rifampin, isoniazid, and ethambutol 3 times weekly for 4 months.
    D. Rifampin, isoniazid, pyrazinamide, and ethambutol 5 times weekly for 2 months followed by rifampin, isoniazid, and pyrazinamide 2 times weekly for 4 months.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-Centered Pharmacotherapy
    a. Task 1: Knowledge statements: 1–7, 10–13, 15; Task 4: Knowledge statements: 2–6

I. HUMAN IMMUNODEFICIENCY VIRUS

A. Transmission of HIV
   1. Sexual transmission
      a. Vaginal, anal, or oral sex
      b. Increases with increased number of sexual partners
   2. Parenteral exposure to blood or blood products
      a. People who inject drugs (PWID): Increased with increased needle sharing
      b. People with hemophilia and recipients of blood transfusions
   3. Perinatal transmission
      a. Antepartum: Through maternal circulation
      b. During delivery
      c. Postpartum: Breastfeeding
      d. Zidovudine therapy decreases the risk of transmission from 23% to 3%–4% (less than 2% with combination therapy). The goal of the Centers for Disease Control and Prevention is to decrease transmissions to less than 1% through suppressive combination antiretroviral therapy (ART) administered throughout pregnancy.

B. Diagnosis
   1. Step 1
      a. Fourth-generation HIV test
      b. Positive: 2–3 weeks after the infection
      c. Negative tests require no further testing; positive tests proceed to step 2.
      d. Sensitivity and specificity: Greater than 99%
      e. Fourth-generation tests: Abbott Architect HIV Ag/Ab Combo Assay; Bio-Rad GS HIV Combo Ag/Ab EIA
   2. Step 2
      a. HIV test that differentiates HIV-1 from HIV-2
      b. If positive: Diagnosis made
      c. If negative or indeterminate: Proceed to step 3
      d. Sensitivity and specificity: Greater than 99%
      e. Multispot HIV-1/HIV-2 Rapid Test
   3. Step 3
      a. HIV-1 nucleic acid amplification test (screening for HIV-1 RNA)
      b. If positive: Diagnosis made
      c. If negative: Negative for HIV-1
      d. HIV-1 NAT tests: APTIMA HIV-1 RNA Qualitative Assay; Procleix Ultrio
   4. Rapid HIV testing
      a. Oral swab or fingerstick
      b. Results within 20 minutes
      c. Negative test result: HIV negative
      d. Positive test result: Repeat with a different manufacturer's test. If positive: HIV positive (refer for appropriate care)
      e. If first test is positive and second test is negative: Repeat with a different manufacturer's test. If positive: HIV positive; if negative: HIV negative
      f. FDA-approved tests: OraQuick Advance, Uni-Gold Recombigen, Chembio SURE CHECK, INSTI HIV, Determine HIV, Chembio DPP, Clearview Stat-Pak

5. Test for HIV RNA (viral load)
    a. Detects HIV RNA in serum (tests for the virus, not for antibodies)
    b. Values expressed as copies of HIV RNA per milliliter or the log of copies of HIV RNA per milliliter
    c. Viral suppression, defined as HIV RNA below the level of detection of the assay (HIV RNA less than 20 copies/mL to 75 copies/mL), is the goal of treatment.
    d. While on treatment, changes greater than 3-fold (about 0.5 log) are statistically significant.
6. Use of HIV RNA testing (viral load)
    a. Most important use of the viral load is to monitor the effectiveness of therapy after initiation of ART.
    b. Newly diagnosed HIV infection (for baseline value to follow)
    c. Every 3–6 months without therapy
    d. From 2 to 4 (no more than 8) weeks after starting or changing therapy (should detect a significant decrease)
    e. Every 3–4 months while on therapy (checking for increase—therapy failure). May consider extension to every 6 months in patients on therapy and suppressed greater than 2 years with immune stability
    f. Whenever there is a clinical event or decrease in CD4 count
7. CD4 T-cell count
    a. Measure of immune function, used to determine the urgency of ART, opportunistic infection prophylaxis, disease progression, and survival
    b. Changes greater than 30% in CD4 counts are considered clinically significant.
    c. CD4 counts decrease, on average, 50–80 cells/mm^3 per year in untreated HIV-infected patients.
    d. With potent combination ART, CD4 counts increase, on average, 50–100 cells/mm^3 per year.
    e. Monitor at diagnosis (baseline), after ART is started to guide discontinuation of opportunistic infection prophylaxis, every 12 months for those consistently on therapy and with CD4 counts between 300 and 500 cells/mm^3 for at least 2 years, and optional if CD4 is greater than 500 cells/mm^3 in those virologically suppressed for at least 2 years. More frequent monitoring (every 3–6 months) may be needed based on clinical symptoms and viral load testing.
8. Who should be screened for HIV?
    a. All patients 13–64 years of age (in all health care settings)
    b. Adults and adolescents at high risk of HIV infection should be checked annually (intravenous drug users, those who have unprotected sex with several partners, men who have sex with men, men or women who have sex for money or drugs, people being treated for sexually transmitted diseases, recipients of several blood transfusions 1975–1985)
    c. Pregnant women – As early as possible and repeat testing in the third trimester

9. AIDS-defining conditions (Table 1)

Table 1. AIDS-Defining Conditions

Bacterial infections, multiple or recurrent (< 6 yr)	Lymphoma: Burkitt (or equivalent term)
Candidiasis: bronchi, trachea, or lungs	Lymphoma: immunoblastic (or equivalent term)
Candidiasis: esophageal	Lymphoma: primary, of brain
Cervical cancer: invasive (≥ 6 yr)	*Mycobacterium avium* complex or *M. kansasii*: disseminated or extrapulmonary
Coccidioidomycosis: disseminated or extrapulmonary	*M. tuberculosis:* any site (pulmonary, disseminated, or extrapulmonary)
Cryptococcosis: extrapulmonary	*Mycobacterium*: other species or unidentified species; disseminated or extrapulmonary
Cryptosporidiosis: chronic intestinal (> 1 mo in duration)	*Pneumocystis jiroveci* pneumonia
Cytomegalovirus disease (other than liver, spleen, or nodes)	Pneumonia: recurrent
Cytomegalovirus retinitis (with loss of vision)	Progressive multifocal leukoencephalopathy
Encephalopathy: HIV related	*Salmonella* septicemia (recurrent)
Herpes simplex: chronic ulcer(s) (> 1 mo in duration); bronchitis, pneumonitis, or esophagitis	Toxoplasmosis of brain
Histoplasmosis: disseminated or extrapulmonary	Wasting syndrome caused by HIV
Isosporiasis: chronic intestinal (> 1 mo in duration)	
Kaposi sarcoma	

C. Prevention of HIV
   1. Universal precautions (Table 2)
      a. Purpose is prevention of parenteral, mucous membrane, and non-intact skin exposures to blood-borne pathogens.
      b. Body fluids

Table 2. Universal Precautions

Universal Precautions Apply to:	Universal Precautions Do Not Apply to:
Blood	Feces
Bodily fluids containing visible blood	Nasal secretions
Semen and vaginal secretions	Sputum
Tissue	Sweat
Cerebrospinal fluid	Tears
Synovial fluid	Urine
Pleural fluid	Vomitus
Peritoneal fluid	Breast milk
Pericardial fluid	Saliva (precautions recommended for dentistry)
Amniotic fluid	

      c. General guidelines
         i. Take care when using and disposing of needles, scalpels, and other sharp instruments.
         ii. Use protective barriers (e.g., gloves, masks, and protective eyewear).
         iii. Wash hands and skin immediately if they are contaminated with body fluids to which universal precautions apply.
   2. Nonpharmacologic prevention
      a. Latex condom
      b. Circumcision (males)

3. Pharmacologic prevention
    a. Pre-exposure prophylaxis (PrEP)
        i. Use in men who have sex with men and heterosexual women and men who recently tested HIV negative with one of the following:
            (a) An HIV-positive sexual partner
            (b) A recent bacterial sexually transmitted infection
            (c) A high number of sex partners
            (d) A history of inconsistent or no condom use
            (e) Commercial sex work
        ii. Use in PWID who recently tested HIV negative with one of the following:
            (a) An HIV-positive injecting partner
            (b) Sharing injection equipment
        iii. Use tenofovir disoproxil fumarate 300 mg plus emtricitabine 200 mg (Truvada) daily; tenofovir alafenamide 25 mg plus emtricitabine 200 mg (Descovy) daily can be used in men and transgender women. "On-demand" dosing is currently being studied.
        iv. Test every 90 days for HIV antibody (and if prophylaxis is discontinued).
        v. Check renal function every 6 months with tenofovir.
    b. Treatment as prevention (TasP)
        i. Maintaining HIV RNA less than 200 copies/mL with ART prevents HIV transmission to sexual partners.
        ii. Other forms of prevention should be used during the first 6 months of treatment and until the HIV RNA is less than 200 copies/mL.
        iii. Adherence is crucial for TasP.
    c. Prevention of maternal-fetal transmission
        i. Pregnant women with HIV not receiving ART
            (a) All HIV-infected pregnant women should receive combination ART; initiate therapy as soon as possible, even in the first trimester.
            (b) Preferred regimens for HIV-infected pregnant women include a dual nucleoside reverse transcriptase inhibitor (NRTI) combination (abacavir/lamivudine, or tenofovir disoproxil fumarate/emtricitabine or lamivudine) and either a ritonavir-boosted protease inhibitor (PI) (atazanavir/ritonavir or darunavir/ritonavir) or an integrase strand transfer inhibitor (INSTI) (raltegravir or dolutegravir).
            (c) All women should have HIV antiretroviral resistance testing completed before starting therapy.
            (d) Continue combination regimen through intrapartum period.
        ii. Pregnant women with HIV receiving potent combination ART
            (a) Continue current combination regimens if already receiving therapy. Consider replacing elvitegravir/cobicistat with raltegravir or a preferred PI combination and using only darunavir twice daily, not once daily. The risk-benefit of using dolutegravir in the first 12 weeks of pregnancy should be discussed with the patient.
            (b) Continue combination regimen through intrapartum period.
        iii. Pregnant women with HIV in labor (with or without therapy during pregnancy)
            (a) Intravenous zidovudine should be administered to HIV-infected women with an HIV RNA greater than 1000 copies/mL (or unknown HIV RNA) near delivery (consider also giving to women with an HIV RNA of 50–1000 copies/mL). Intravenous zidovudine is not necessary for HIV-infected women with an HIV RNA of 50 copies/mL or less during late pregnancy and near delivery and no concerns about adherence to the combination ART regimen.
            (b) Continue combination ART as much as possible during labor.

iv. Infants born to mothers who are HIV positive
(a) Low risk of perinatal HIV transmission: Zidovudine 4 mg/kg/dose every 12 hours for 4 weeks, initiated within 6–12 hours of delivery
(b) Higher risk of perinatal transmission or presumed HIV exposure: Presumptive HIV therapy with zidovudine, lamivudine, and nevirapine OR zidovudine, lamivudine, and raltegravir. Presumptive therapy should continue for 6 weeks.

d. Post-exposure prophylaxis (PEP)
i. Use universal precautions.
ii. Post-exposure prophylaxis can reduce HIV infection by about 80%.
iii. Nonoccupational exposures
(a) Treat if exposure of vagina, rectum, eye, mouth, mucous membrane, or non-intact skin with blood, semen, vaginal secretions, or breast milk of a person with a known HIV infection
(b) Begin prophylaxis within 72 hours. Treatment should be administered for 4 weeks.
(c) Preferred regimen: Raltegravir twice daily or dolutegravir daily plus tenofovir/emtricitabine daily (do not use dolutegravir in women who are potentially pregnant or early in their pregnancy)
(d) Alternative regimen: Darunavir/ritonavir daily plus tenofovir/emtricitabine daily
iv. Occupational exposures
(a) Needlesticks or cuts (1 in 300 risk) and mucous membrane exposure (1 in 1000 risk)
(b) Begin treatment within hours; if HIV status of source patient is unknown, start treatment while status is being evaluated. Treatment should be administered for 4 weeks.
(c) Preferred regimen: Raltegravir twice daily or raltegravir HD once daily or dolutegravir once daily plus tenofovir disoproxil fumarate/emtricitabine or lamivudine
(d) Alternative regimens:
(1) One of the following agents: Raltegravir, darunavir/ritonavir, etravirine, rilpivirine, atazanavir/ritonavir, or lopinavir/ritonavir plus one of the following combinations: tenofovir/emtricitabine, tenofovir/lamivudine, zidovudine/lamivudine, or zidovudine/emtricitabine
(2) Elvitegravir, cobicistat, tenofovir, emtricitabine (Stribild)

D. Treatment of HIV
1. Reverse transcriptase inhibitors (RTIs) (nucleoside [NRTIs], nucleotide, and nonnucleoside [NNRTIs])
a. Reverse transcriptase: Enzyme needed to copy viral RNA to DNA
b. See Tables 3 and 4 for RTI characteristics.
2. Protease inhibitors (PIs)
a. Protease: Enzyme needed to cleave polyproteins into mature viral protein components
b. See Table 5 for PI characteristics.
3. Integrase inhibitors (INSTIs)
a. Integrase: Enzyme needed for integration of viral DNA into the host cellular genome
b. See Table 6 for INSTI characteristics.
4. Entry and post-attachment inhibitors
a. Block binding and/or entry of the virus into human cells
b. See Table 7 for entry and post-attachment inhibitor characteristics.

Table 3. Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

	Abacavir (Ziagen)	Emtricitabine (Emtriva)	Lamivudine (Epivir)	Zidovudine (AZT, Retrovir)	Tenofovir Disoproxil Fumarate (Viread)	Tenofovir Alafenamide (Vemlidy)
RTI type	Nucleoside	Nucleoside	Nucleoside	Nucleoside	Nucleotide	Nucleotide
Form	300-mg tablets 20 mg/mL liquid Trizivir: 300 mg ABC/150 mg 3TC/ 300 mg ZDV Triumeq: 600 mg ABC/ 50 mg DTG/ 300 mg 3TC Epzicom (see Lamivudine)	200-mg capsules 10 mg/mL liquid Truvada: 200 mg FTC/300 mg TDF Atripla (see Efavirenz) Complera (see Rilpivirine) Stribild (see Elvitegravir) Genvoya (see Elvitegravir) Biktarvy (see Bictegravir) Symtuza (see Darunavir)	150-, 300-mg tablets 10 mg/mL liquid Combivir: 150 mg 3TC/300 mg ZDV Epzicom: 300 mg 3TC/600 mg ABC Cimduo/Temixys: 300 mg 3TC/300 mg TDF Dovato (see Dolutegravir) Symfi (see Efavirenz) Trizivir (see Abacavir) Delstrigo (see Doravirine)	100-mg capsules, 300-mg tablets 50 mg/5 mL liquid 10 mg/mL injection	300-mg tablets Truvada: 200 mg FTC/300 mg TDF Cimduo/Temixys (see Lamivudine) Atripla (see Efavirenz) Complera (see Rilpivirine) Stribild (see Elvitegravir) Delstrigo (see Doravirine)	25-mg tablets Descovy: 200 mg FTC/ 25 mg TAF Odefsey (see Rilpivirine) Genvoya (see Elvitegravir) Biktarvy (see Bictegravir) Symtuza (see Darunavir)
Dosing	300 mg BID or 600 mg daily[a]	200 mg daily or 240 mg liquid daily[b]	150 mg BID or 300 mg daily < 50 kg: 4 mg/kg BID[b]	200 mg TID or 300 mg BID[b]	300 mg daily[c]	25 mg daily[c]; 10 mg daily with cobicistat
Oral bioavailability	82%	93%	86%	60%	40% Take with food	Take with food
Serum half-life (hr)	1.5	10	13–19	1.1	10–14	0.5
Intracellular half-life (hr)	12–26	> 20	18–22	7	> 60	150–180
Elimination	Metabolized by alcohol dehydrogenase and glucuronyltransferase Metabolites; renal	Renal excretion (86%)	Renally excreted unchanged (70%)	Metabolized to ZDV glucuronide (GZDV) Renal excretion of GZDV	Eliminated by renal filtration and active secretion	Eliminated primarily in urine and feces
Adverse drug reactions	Hypersensitivity reaction (including fever, rash, nausea, vomiting, diarrhea, malaise, fatigue, respiratory symptoms – screen for *HLA-B*5701*), increased risk of myocardial infarction	Minimal toxicity; skin hyperpigmentation	Minimal toxicity	Bone marrow suppression, nausea, vomiting, headache, insomnia, asthenia, nail pigmentation, myalgia, lactic acidosis/hepatic steatosis	Diarrhea, nausea, vomiting, headache, loss of bone mineral density, renal toxicity, more favorable effects on lipids than TAF	Diarrhea, nausea, headache, fewer effects on bone mineral density and renal function, more favorable effects on bone and kidneys than TDF
Drug interactions	ABC increases methadone clearance			Myelosuppressive agents Methadone, atovaquone increases ZDV		Carbamazepine, oxcarbazepine, phenytoin, phenobarbital Rifampin, rifabutin, rifapentine St. John's wort

[a]Dosage adjustment in hepatic insufficiency.

[b]Dosage adjustment in renal insufficiency.

[c]Dosage adjustment/avoid use in renal insufficiency: TDF < 50–70 mL/min; TAF < 30 mL/min.

ABC = abacavir; AZT = azidothymidine (zidovudine); BID = twice daily; FTC = emtricitabine; RTI = reverse transcriptase inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; 3TC = lamivudine; TID = three times daily; ZDV = zidovudine.

Table 4. Nonnucleoside Reverse Transcriptase Inhibitors

	Doravirine (Pifeltro)	Efavirenz (Sustiva)	Etravirine (Intelence)	Nevirapine (Viramune)	Rilpivirine (Edurant)
Form	100-mg tablets Delstrigo: 300 mg 3TC/ 300 mg TDF/doravirine 100 mg	50-, 200-mg capsules 600-mg tablets Atripla: 200 mg FTC/ 300 mg TDF/ ERV 600 mg Symfi: 600 mg EFV/300 mg 3TC/ 300 mg TDF	100-, 200-mg tablets	200-mg tablets 400-mg XR tablets 50 mg/5 mL suspension	25-mg tablets Complera: 200 mg FTC/ 300 mg TDF/RPV 25 mg Odefsey: 200 mg FTC/25 mg TAF/RPV 25 mg Juluca: 25 mg RPV/50 mg DTG
Dosing	100 mg daily	400–600 mg nightly	200 mg BID	200 mg daily for 14 days, then 200 mg BID or 400 mg daily (XR)[a,b]	25 mg daily
Oral bioavailability	64% Take with or without food	42% Avoid with high-fat meal	Take with food	> 90%	Take with food
Serum half-life (hr)	15	40–55	41	25–30	50
Elimination	Metabolized by CYP3A4, 6% excreted in urine	Metabolized by CYP2B6 and CYP3A4; 14%–34% excreted in urine, 16%–61% in feces	Metabolized by CYP3A4, CYP2C9, CYP2C19	Metabolized by CYP3A4; 80% excreted in urine (< 5% unchanged), 10% in feces	Metabolized by CYP3A4
Adverse drug reactions	Rash, nausea, diarrhea, abdominal pain, headache CNS symptoms (fatigue, dizziness, insomnia, abnormal dreams, somnolence) – less than with EFV	Rash, CNS symptoms (insomnia, impaired concentration, nightmares, mania), elevated LFTs, hyperlipidemia	Rash, nausea, hypersensitivity reaction	Rash, GI toxicity, elevated LFTs; hepatotoxicity	Rash, CNS symptoms (depression, insomnia, headache) – less than with EFV
Drug interactions	Avoid CYP3A inducers	Induces CYP3A4 and CYP2B6	Induces CYP3A4 Inhibits CYP2C9 and CYP2C19	Induces CYP3A4 Avoid strong CYP3A inducers and inhibitors	PPIs (contraindicated), histamine-2 blockers, antacids Avoid CYP3A inducers

[a]Dosage adjustment in hepatic insufficiency.

[b]Dosage adjustment in renal insufficiency.

CNS = central nervous system; CYP = cytochrome P450; DOR = doravirine; EFV = efavirenz; ETR = etravirine; LFT = liver function test; NVP = nevirapine; PPI = proton pump inhibitor; RPV = rilpivirine; XR = extended release.

Table 5. Protease Inhibitors

	Atazanavir (Reyataz)	Darunavir (Prezista)	Lopinavir/Ritonavir (Kaletra)	Ritonavir (Norvir)
Form	100-, 150-, 200-, 300-mg capsules Evotaz: 300 mg/cobicistat (COBI) 150-mg tablets	75-, 150-, 300-, 400-, 600-mg tablets Prezcobix: 800 mg/COBI 150-mg tablets	100/25-, 200/50-mg tablets; 80/20 mg/mL solution	100-mg tablets; 80 mg/mL liquid
Dosing	ATV 400 mg daily[a,b] or ATV 300 mg with RTV 100 mg daily or ATV 300 mg with COBI 150 mg daily ATV alone not recommended in antiretroviral-experienced patients If taking TDF but not EFV: ATV 300 mg + RTV 100 mg daily If taking EFV: ATV 400 mg + RTV 100 mg daily	800 mg with RTV 100 mg daily or 600 mg with RTV 100 mg BID[a] DRV 800 mg + COBI 150 mg daily	400/100 mg BID or 800/200 mg daily with food If taking efavirenz or nevirapine: 500 mg/125 mg BID	"Boosting dose" = 100–400 mg divided once or twice daily
Oral bioavailability	Food increases absorption and bioavailability; take with food	Food increases absorption and bioavailability; take with food	Take solution with food; take tablets without respect to food	65%–75%; take with food
Serum half-life (hr)	7	15	56	35
Elimination	CYP3A4	CYP3A4	CYP3A4	CYP3A4 > CYP2D6 > CYP2C9/10
Adverse drug reactions	Indirect hyperbilirubinemia rash, elevated transaminases, nephrolithiasis, prolonged PR interval and heart block, endocrine disturbances[c]	Rash (sulfa); hepatotoxicity; endocrine disturbances[c]	GI intolerance; fatigue; asthenia; pancreatitis; PR and QTc prolongation; endocrine disturbances[c]	GI intolerance; paresthesias (circumoral and extremities); taste disturbances; asthenia; endocrine disturbances[c]
Drug interactions	Inhibits CYP3A4, PPIs, histamine-2 blockers, antacids Inhaled corticosteroids	Inhibits CYP3A4 Inhaled corticosteroids	Inhibits CYP3A4, CYP2D6 Inhaled corticosteroids	Inhibits CYP3A4, CYP2D6 (potent) Induces glucuronyltransferases Inhaled corticosteroids

[a]Dosage adjustment in hepatic insufficiency.

[b]Dosage adjustment in renal insufficiency.

[c]Endocrine disturbances include insulin resistance (type 2 diabetes in 8%–10%), peripheral fat loss and central fat accumulation (in 50%), and lipid abnormalities (in 70%).

ATV = atazanavir; DRV = darunavir; GI = gastrointestinal; LPV/r = lopinavir/ritonavir; RTV = ritonavir.

Table 6. Integrase Strand Transfer Inhibitors

	Bictegravir	Dolutegravir (Tivicay)	Elvitegravir	Raltegravir (Isentress)	Cabotegravir
Form	Biktarvy: BIC 50 mg/TAF 25 mg/FTC 200 mg	10-, 25-, 50-mg tablets Tivicay PD: 5-mg tablets for oral suspension Triumeq: 600 mg ABC/ 50 mg DTG/300 mg 3TC Dovato: 50 mg DTG/ 300 mg 3TC Juluca (see Rilpivirine)	Stribild: EVG 150 mg/ cobicistat 150 mg/TDF 300 mg/FTC 200 mg Genvoya: Same as Stribild except 10 mg of TAF instead of TDF	25-, 100-, 400-mg tablets; Isentress HD: 600-mg tablets	Cabenuva: 400 mg CAB/ 600 mg RPV, 600 mg CAB/ 900 mg RPV extended release injectable suspension Vocabria: 30 mg tablets
Dosing	50 mg once daily[a,b]	50 mg once daily[a]	Stribild: Once daily[a,b] Genvoya: Once daily[a,b]	400 mg BID Isentress HD: 1200 mg daily	30 mg oral daily for 1 month, then 600mg/900mg IM once then 400mg/600mg IM monthly
Oral bioavailability	Take with or without food	Take with or without food	Food increases absorption and bioavailability Take with food	Not established	N/A
Serum half-life (hr)	18	14	13	9	5.6-11.5 (CAB)/13-28 (RPV) weeks
Elimination	Metabolized by CYP3A and glucuronidation by UGT1A1	Metabolized by glucuronidation by UGT1A1/3 enzymes and by CYP3A	Metabolized by CYP3A and glucuronidation by UGT1A1/3 enzymes Cobicistat is metabolized by CYP3A and CYP2D6	Metabolized by hepatic glucuronidation by UGT1A1	Metabolized by hepatic glucuronidation by UGT1A1
Adverse drug reactions	Nausea, diarrhea, headache, weight gain Benign increases in creatinine (inhibits creatinine secretion) and bilirubin (blocks bilirubin clearance)	Insomnia, headache, weight gain, hepatotoxicity Benign increases in creatinine (inhibits creatinine secretion) and bilirubin (blocks bilirubin clearance)	Nausea, diarrhea Cobicistat: Benign increases in creatinine (inhibits creatinine secretion) and bilirubin (blocks bilirubin clearance)	Nausea, diarrhea, rash, headache, pyrexia, creatine kinase elevation, insomnia, weight gain Benign increases in creatinine (inhibits creatinine secretion) and bilirubin (blocks bilirubin clearance)	Injection site reactions, fever, fatigue, pain
Drug interactions	Watch CYP3A and UGT1A1 inducers and inhibitors. Avoid rifampin, other rifamycins, St. John's wort, and certain anticonvulsants Dofetilide Divalent and trivalent cations	Inhibitors and inducers of UGT1A3, UGT1A9, BCRP, and P-glycoprotein. Avoid rifampin, rifapentine, certain anticonvulsants, St. John's wort Divalent and trivalent cations Dofetilide	Monitor closely if used with CYP3A inducers or inhibitors. Avoid rifampin, other rifamycins, certain anticonvulsants, St. John's wort Divalent and trivalent cations Inhaled corticosteroids Dofetilide, eplerenone, ivabradine, ranolazine	Inducers of UGT1A1: Rifampin, rifapentine, efavirenz, tipranavir/ ritonavir, certain anticonvulsants Divalent and trivalent cations	Inducers of UGT1A1: Rifampin, rifapentine, efavirenz, tipranavir/ ritonavir, certain anticonvulsants

[a]Dosage adjustment in hepatic insufficiency.

[b]Dosage adjustment in renal insufficiency.

BCRP=breast cancer resistance protein; BIC=bictegravir; CAB=cabotegravir; DTG=dolutegravir; EVG=elvitegravir; RAL=raltegravir; UGT=uridine diphosphate (UDP)-glucuronosyltransferase.

Table 7. Entry Inhibitors

	Enfuvirtide (Fuzeon)	Ibalizumab (Trogarzo)	Maraviroc (Selzentry)	Fostemsavir (Rukobia)
Class	Entry inhibitor	Post-attachment inhibitor	Entry inhibitor	Attachment inhibitor
Mechanism of action	Attachment of gp120 to CD4 receptor and coreceptors CCR5 or CXCR4 results in exposure of the specific peptide sequence of gp41; enfuvirtide binds to this gp41 peptide sequence, preventing fusion	Blocks HIV from binding to the domain 2 of CD4 and interfering with post-attachment steps required for HIV-1 entry	Binds to the CCR5 receptor of the CD4 T cell, preventing fusion and HIV entry	Converted to temsavir, which binds to the gp120 subunit of gp160, preventing the virus from interacting with CD4 receptors
Form	90-mg vials	200-mg vials	150-, 300-mg tablets	600-mg tablets
Dosing	90 mg SC BID	2000 mg IV × 1, followed by 800 mg IV every 2 wk	150–600 mg BID (depending on concomitant drug interactions)[a]	600 mg BID
Oral bioavailability	N/A	N/A	23%–33%	27%
Serum half-life (hr)	3.8	64	14–18	11
Elimination	Metabolized by hydrolysis		Metabolized by CYP3A	Metabolized by esterases and CYP3A4
Adverse drug reactions	Hypersensitivity reactions; local injection site reactions (98%); pneumonia	Diarrhea, dizziness, nausea, rash. Elevations in bilirubin, creatinine, glucose, lipase. Blood dyscrasias	Abdominal pain, cough, dizziness, musculoskeletal symptoms, pyrexia, rash, upper respiratory tract infections, hepatotoxicity, orthostatic hypotension	Nausea, diarrhea, abdominal pain, headache, fatigue, rash, sleep disturbances. Elevations in LFTs and creatinine. May prolong QTc
Drug interactions	None	None	CYP3A substrate (watch CYP3A inducers and inhibitors)	CYP3A4 substrate (watch CYP3A4 inducers and inhibitors)

[a]Dosage adjustment in renal insufficiency.

FTR = fostemsavir; gp = glycoprotein; IBA = ibalizumab; IV = intravenous(ly); MVC = maraviroc; N/A = not applicable; SC = subcutaneous(ly); T20 = enfuvirtide.

Patient Case

1. F.G. is a 27-year-old man who is HIV positive but asymptomatic. His CD4 count is 550 cells/mm^3, and his viral load is 5000 copies/mL by reverse transcriptase polymerase chain reaction. Which is the best treatment for F.G.?

   A. ART should not be given because his CD4 count is still above 500 cells/mm^3.

   B. Initiate emtricitabine/tenofovir only because his CD4 count is still above 500 cells/mm^3.

   C. Initiate combination therapy of abacavir, lamivudine, and atazanavir/ritonavir.

   D. Initiate combination therapy of tenofovir, emtricitabine, and raltegravir.

5. Treatment of the patient who is HIV positive
   a. Guidelines recommend HIV treatment for all infected patients, regardless of CD4 count (AI).
   b. Recommended initial regimens for most patients with HIV: The optimal ART for a treatment-naive patient consists of two NRTIs in combination with an INSTI.
      i. Bictegravir/tenofovir alafenamide/emtricitabine
      ii. Dolutegravir/abacavir/lamivudine; only for patients who are *HLA-B*5701* negative
      iii. Dolutegravir plus tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine
      iv. Raltegravir plus tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine
   c. Recommended initial regimens in certain clinical situations:
      i. NNRTI-based regimens
         (a) Doravirine/tenofovir disoproxil fumarate/lamivudine or doravirine plus tenofovir alafenamide/emtricitabine
         (b) Efavirenz/tenofovir disoproxil fumarate/emtricitabine
         (c) Efavirenz plus tenofovir alafenamide/emtricitabine
         (d) Rilpivirine/tenofovir disoproxil fumarate/emtricitabine or rilpivirine/tenofovir alafenamide/emtricitabine; only for patients with viral load less than 100,000 copies/mL and CD4 count greater than 200 cells/mm^3
      ii. PI-based regimens
         (a) Atazanavir/ritonavir or Atazanavir/cobicistat plus tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine; if TDF, not recommended for CrCl less than 70 mL/minutes/1.73 m^2
         (b) Darunavir/ritonavir or darunavir/cobicistat plus abacavir/lamivudine; only for patients who are *HLA-B*5701* negative
         (c) Darunavir/ritonavir or darunavir/cobicistat plus tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine; if TDF, not recommended for CrCl less than 70 mL/minutes/1.73 m^2
      iii INSTI-based regimens:
         (a) Elvitegravir/cobicistat/tenofovir disoproxil fumarate /emtricitabine or elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine; only for patients with pre-ART CrCl greater than 70 mL/minute/1.73 m^2 if using tenofovir disoproxil fumarate or greater than 30 mL/minute/1.73 m^2 if using tenofovir alafenamide
      iv. Regimens to consider when ABC, TAF and TDF cannot be used:
         (a) Dolutegravir plus lamivudine
         (b) Darunavir/ritonavir plus raltegravir (only if HIV RNA less than 100,000 copies/mL and CD4 greater than 200/mm^3);
         (c) Darunavir/ritonavir plus lamivudine

Patient Case

2. Six months after F.G. (from patient case 1) starts appropriate therapy, his CD4 count is 720 cells/mm^3, and his viral load is undetectable. Two years later, his CD4 count decreases to 310 cells/mm^3, and his viral load is 15,000 copies/mL. Resistance testing detects resistance to raltegravir. His HIV regimen is changed to abacavir, lamivudine, and darunavir/ritonavir. Which of the following tests must be performed before starting abacavir?
   A. Liver function tests because of the risk of hepatotoxicity.
   B. *HLA-B*5701* allele screening because of the risk of a serious hypersensitivity reaction.
   C. Hemoglobin A1C and a lipid panel because of the risk of endocrine disturbances.
   D. Bilirubin because of the risk of hyperbilirubinemia.

II. OPPORTUNISTIC INFECTIONS: PATIENTS WITH HIV

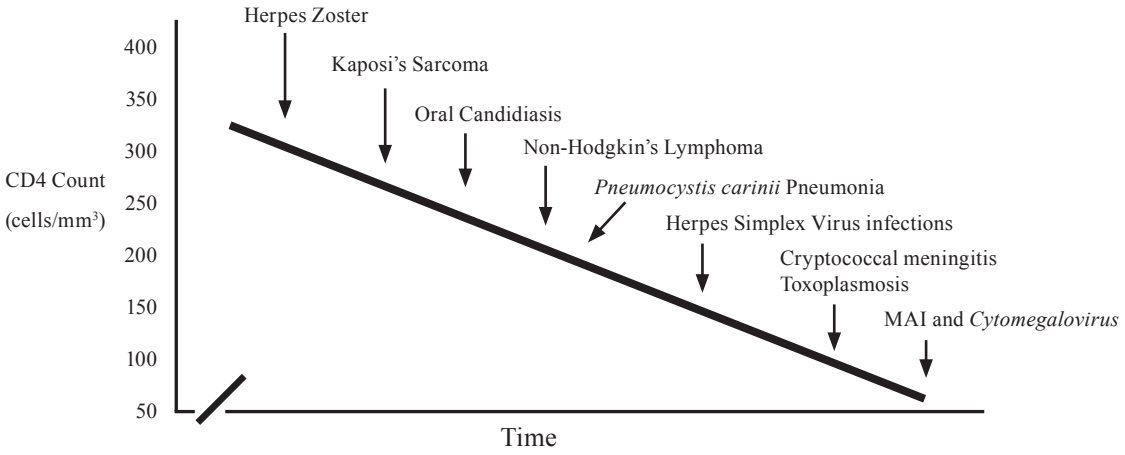

Figure 1. Relationship between CD4 count and risk of HIV-related opportunistic infections.
MAI = *Mycobacterium avium-intracellulare.*

A. Initiating Potent Combination ART in the Setting of Acute Opportunistic Infections
   1. Opportunistic infections with no effective therapy require prompt initiation of ART: cryptosporidiosis, microsporidiosis, promyelocytic leukemia, and Kaposi sarcoma.
   2. ART should begin within 2 weeks of acute opportunistic infections, except for tuberculosis (TB), in which therapy should begin within 2 weeks when the CD4 count is less than 50 cells/mm^3 and by 8–12 weeks for all others, and cryptococcal meningitis, in which therapy should begin 5 weeks after diagnosis (because of immune reconstitution inflammatory syndrome [IRIS]).

B. *Pneumocystis jiroveci* (formerly *carinii*) Pneumonia (PCP)
   1. Clinical presentation
      a. Fever, shortness of breath, and nonproductive cough
      b. Elevated lactate dehydrogenase
      c. Diffuse pulmonary infiltrates
      d. In general, with CD4 counts less than 200 cells/mm^3
      e. Hypoxemia with elevated alveolar-arterial (A-a) gradient and decreased P_{O_2}; A-a gradient = 150 − P_{O_2} − P_{CO_2}

Patient Cases

3. Three years later, F.G. (from patient cases 1–2) has not responded to any of his ART regimens because of resistance or intolerance. His CD4 count has decreased to 135 cells/mm^3. For which infection is it most important that F.G. receive primary prophylaxis?
   A. *Pneumocystis jiroveci* pneumonia (PCP, PJP).
   B. Cryptococcal meningitis.
   C. Cytomegalovirus (CMV).
   D. *Mycobacterium avium* complex (MAC).

4. B.L. is a 44-year-old HIV-positive man who arrives at the emergency department severely short of breath. He is an extremely nonadherent patient and has not seen a health care provider in more than 3 years. A chest radiograph shows pulmonary infiltrates in both lung fields. The results of the laboratory tests are as follows: sodium 147 mEq/L, potassium 4.2 mEq/L, chloride 104 mEq/L, bicarbonate 25.2 mEq/L, glucose 107 mg/dL, blood urea nitrogen 38 mg/dL, serum creatinine 1.1 mg/dL, aspartate aminotransferase 28 IU/L, alanine aminotransferase 32 IU/L, lactate dehydrogenase 386 IU/L, alkaline phosphate 75 IU/L, pH 7.45, P_{O_2} 63 mm Hg, P_{CO_2} 32 mm Hg, and oxygen saturation 85%. His CD4 count is 98 cells/mm^3. Sputum Gram stain is negative, as is silver stain. Which is the best therapy for B.L.?
   A. Pentamidine intravenously with adjuvant prednisone therapy for 21 days.
   B. Trimethoprim/sulfamethoxazole orally for 21 days.
   C. Trimethoprim/sulfamethoxazole intravenously with adjuvant prednisone therapy for 21 days.
   D. Atovaquone orally for 21 days.

2. Diagnosis
   a. Induced sputum or bronchoalveolar lavage or transbronchial biopsy
   b. Methenamine silver stain of sputum sample
3. Therapy
   a. Trimethoprim/sulfamethoxazole (preferred)
      i. Dose: 15–20 mg/kg/day of trimethoprim divided every 6–8 hours for 21 days (intravenously for moderate to severe PCP); trimethoprim/sulfamethoxazole double strength 2 tablets three times daily or weight based (for mild to moderate PCP)
      ii. Adverse effects (80% of patients, with 20%–60% requiring discontinuation)
         (a) Nausea and vomiting
         (b) Rash
         (c) Anemia, thrombocytopenia, leucopenia
         (d) Renal impairment or hyperkalemia (also, small increases in serum creatinine occur because of competition between trimethoprim and creatinine for renal secretion)
      iii. Prophylactic dose
         (a) Preferred: Trimethoprim/sulfamethoxazole double strength or single strength once daily (pediatric dose, 150 mg/m^2 per dose of trimethoprim and 750 mg/m^2 per dose of sulfamethoxazole)
         (b) Alternative: Trimethoprim/sulfamethoxazole double strength three times/week
   b. Clindamycin and primaquine (alternative)
      i. Dose: Clindamycin 600 mg every 6 hours or 900 mg every 8 hours intravenously plus primaquine 30 mg daily (for moderate to severe disease) or 450 mg every 6 hours or 600 mg every 8 hours orally and primaquine base 30 mg/day for 21 days (for mild to moderate disease)

ii. Adverse effects
(a) Rash
(b) Anemia, methemoglobinemia (test for glycose-6-phosphate dehydrogenase [G6PD] deficiency)
(c) Diarrhea

c. Pentamidine (alternative)
i. Dose: 4 mg/kg/day intravenously for 21 days (for moderate to severe disease)
ii. Adverse effects
(a) Hypotension
(b) Rash
(c) Electrolyte disturbances
(d) Hypoglycemia or hyperglycemia
(e) Pancreatitis
iii. Prophylactic dose: 300 mg by nebulization (Respirgard) once monthly (can predose with β-agonist to diminish respiratory irritation)

d. Trimethoprim and dapsone (alternative)
i. Dose: 15 mg/kg/day of trimethoprim divided every 8 hours and dapsone 100 mg/day for 21 days (only for mild to moderate PCP)
ii. Adverse effects
(a) Nausea and vomiting
(b) Anemia (test for G6PD deficiency)
iii. Prophylactic dose: Dapsone 100 mg/day (pediatric dose, 1 mg/kg/day) alone or 50 mg/day or 200 mg/week with 50–75 mg of pyrimethamine and 25 mg of leucovorin weekly

e. Atovaquone (Mepron) (alternative)
i. Dose: 750 mg twice daily for 21 days given with a high-fat meal (only for mild to moderate PCP)
ii. Pediatric dose (less than 40 kg [88 lb]) = 40 mg/kg/day divided twice daily
iii. Equal to trimethoprim/sulfamethoxazole for PCP but not an antibacterial
iv. Potential for decreased efficacy in patients with diarrhea (because of poor absorption)
v. Adverse effects
(a) Nausea and vomiting
(b) Rash
(c) Transient increase in liver function tests
(d) Insomnia, headache, fever
vi. Prophylactic dose = 1500 mg once daily

f. Adjuvant therapy: Corticosteroids
i. Used in patients with severe PCP (A-a gradient of 35 or more or Po_2 of 70 mm Hg or less); start within 72 hours
ii. Decreases mortality
iii. Dose: 40 mg twice daily of prednisone for 5 days, followed by 40 mg/day for 5 days, and then 20 mg/day for remainder of PCP therapy (use cautiously in patients with TB)

4. Prophylaxis
a. Secondary prophylaxis in patients after PCP (may be discontinued if CD4 count is more than 200 cells/mm^3 for 3 months or longer because of potent combination ART)
b. Primary prophylaxis in patients with CD4 count less than 200 cells/mm^3 (may be discontinued if CD4 count is more than 200 cells/mm^3 for 3 months or longer because of potent combination ART)
c. Consider stopping primary or secondary prophylaxis in patients with CD4 counts of 100-200 cells/mm^3 if HIV plasma RNA level is below limits of detection for at least 3-6 months.

C. Toxoplasmosis
   1. Description
      a. *Toxoplasma gondii* (protozoan)
      b. Felines are the hosts for sporozoite production (change litter box daily, wash hands after changing litter box or have someone else change the litter box, and, ideally, keep the cat indoors).
      c. From 15% to 68% of adults in the United States are seropositive for *T. gondii*.
      d. Secondary to undercooked beef, lamb, pork, or raw shellfish (stress avoidance in patients with HIV)
      e. Case-defining illness in 2.1% of patients with AIDS
   2. Signs and symptoms
      a. Fever, headache, altered mental status
      b. Focal neurologic deficits (60%): Hemiparesis, aphasia, ataxia, visual field loss, nerve palsies
      c. Seizures (33%)
      d. CSF: Mild pleocytosis, increased protein, normal glucose
   3. Diagnosis
      a. Brain biopsy: Only definitive diagnosis but generally reserved for patients who do not respond to specific therapy or when other workup suggests an etiology other than toxoplasmosis
      b. Antibodies or *T. gondii* isolation in serum or CSF
      c. Magnetic resonance imaging scan or computed tomographic scan: Multiple, bilateral, hypodense, ring-enhancing mass lesions (magnetic resonance imaging scan more sensitive than computed tomographic scan)
   4. Therapy
      a. Preferred therapy
         i. Pyrimethamine 50–75 mg/day (loading dose of 200 mg) *plus*
         ii. Sulfadiazine 1000–1500 mg every 6 hours (watch crystalluria)
            (a) Bone marrow suppression: Thrombocytopenia, granulocytopenia, anemia
            (b) Add folinic acid (leucovorin) 10-25 mg/day to reduce bone marrow effects of pyrimethamine.
            (c) Duration: 6 weeks or after signs and symptoms resolve
      b. Alternative therapy
         i. Clindamycin 600 mg intravenously or orally every 6 hours plus pyrimethamine (see above) – Use for sulfa intolerance or nonresponse to preferred therapy
         ii. Trimethoprim/sulfamethoxazole 5 mg/kg of trimethoprim intravenously or orally twice daily
         iii. Atovaquone 1500 mg orally twice daily plus pyrimethamine/leucovorin (see above)
         iv. Atovaquone 1500 mg orally twice daily plus sulfadiazine (see above)
         v. Atovaquone 1500 mg orally twice daily
   5. Prophylaxis
      a. Relapse rates approach 80% without maintenance therapy.
      b. Toxoplasma-seropositive patients with a CD4 count of 100 cells/mm^3 or less should receive primary prophylaxis.
      c. Primary prophylaxis
         i. Trimethoprim/sulfamethoxazole double strength once daily or dapsone/pyrimethamine/leucovorin or atovaquone with or without pyrimethamine at doses used for PCP prophylaxis
         ii. May be discontinued if the CD4 count is more than 200 cells/mm^3 for 3 months or longer because of potent combination ART
         iii. Consider stopping primary prophylaxis in patients with CD4 counts of 100-200 cells/mm^3 if HIV plasma RNA level is below limits of detection for at least 3-6 months.

d. Secondary prophylaxis
    i. Pyrimethamine 25–50 mg/day plus leucovorin 10–25 mg/day with sulfadiazine 2–4 g/day
    ii. Clindamycin 600 mg orally every 8 hours plus pyrimethamine (see above) – Use for sulfa intolerance or non-response to preferred therapy.
    iii. Trimethoprim/sulfamethoxazole double strength orally twice daily
    iv. Atovaquone 750–1500 mg orally twice daily plus pyrimethamine/leucovorin (see above)
    v. Atovaquone 750–1500 mg orally twice daily plus sulfadiazine (see above)
    vi. Atovaquone 750–1500 mg orally twice daily
    vii. May be discontinued if the CD4 count is more than 200 cells/mm^3 and patient is asymptomatic for 6 months or longer because of potent combination ART

D. *Candida* Infections
1. Oral *Candida* infections (thrush)
    a. More than 90% of patients with AIDS sometime during their illness
    b. Signs and symptoms
        i. Creamy white, curdlike patches on the tongue and other oral mucosal surfaces
        ii. Pain; decreased food and fluid intake
2. *Candida* esophagitis
    a. Not always an extension of oral thrush (30% do not have oral thrush)
    b. Signs and symptoms: Painful swallowing, obstructed swallowing, substernal pain
3. Diagnosis
    a. Signs and symptoms of infection
    b. Fungal cultures, potassium hydroxide smear
    c. Endoscopic evaluation
4. Therapy
    a. Oropharyngeal candidiasis (treat 7–14 days)
        i. Fluconazole 100 mg orally daily.
        ii. Alternative: Itraconazole solution 200 mg orally daily or posaconazole suspension 400 mg orally daily (after twice daily on day 1) or miconazole buccal tablets 50 mg orally daily or clotrimazole troches 10 mg orally five times daily or nystatin 5 mL (100,000 units/mL): swish and swallow four or five times daily
    b. Esophageal candidiasis (treat 14–21 days)
        i. Fluconazole 100–400 mg orally or intravenously daily or itraconazole solution 200 mg orally daily
        ii. Alternative: Voriconazole, caspofungin, micafungin, anidulafungin, amphotericin B deoxycholate, lipid formulation of amphotericin B, posaconazole or isavuconazole
    c. Vulvovaginal candidiasis
        i. Fluconazole 150 mg orally for one dose or topical azoles for 3–7 days
        ii. Alternative: Itraconazole solution 200 mg orally daily for 3–7 days

E. Cryptococcosis
1. *Cryptococcus neoformans*
2. Occurs in 6%–10% of patients with AIDS
3. In general, occurs in patients with CD4 counts less than 50 cells/mm^3
4. Acute mortality is 10%–25%, and 12-month mortality is 30%–60%.
5. Worldwide distribution
    a. Found in aged pigeon droppings and nesting places (e.g., barns, window ledges)
    b. Organism must be aerosolized and inhaled; it then disseminates hematogenously.

Patient Cases

5. G.H. is a 33-year-old HIV-positive man who presents to the clinic with a severe headache that has gradually worsened during the past 3 weeks. He also has memory problems and is always tired. He has refused ART in the past, and his most recent CD4 count was 75 cells/mm^3. He is given a diagnosis of cryptococcal meningitis. Which is the best treatment for G.H.?
   A. Amphotericin B deoxycholate 0.7–1 mg/kg/day plus fluconazole 800 mg daily for 2 weeks, followed by fluconazole 400 mg/day for 8 weeks. Begin ART in the first 1–2 weeks of therapy.
   B. Liposomal amphotericin B 3–4 mg/kg/day plus flucytosine 25 mg/kg every 6 hours for 2 weeks, followed by fluconazole 400 mg/day for 8 weeks. Begin ART after 5 weeks of antifungal therapy.
   C. Fluconazole 1200 mg/day for 10–12 weeks. Begin ART fluconazole 800 mg daily.
   D. Lipid-formulated amphotericin B 3–4 mg/kg/day plus fluconazole 800 mg/day for 2 weeks, followed by fluconazole 400 mg/day for 8 weeks. Begin ART in the first 1-2 weeks of therapy.

6. After being treated for cryptococcal meningitis, G.H. is initiated on potent combination ART. For 2, 6, and 8 months after starting the therapy, his CD4 counts are 212, 344, and 484 cells/mm^3, respectively. Which is the best follow-up therapy for G.H. now?
   A. Continue fluconazole maintenance therapy.
   B. Give maintenance therapy with fluconazole for at least 1 year; then, it can be discontinued because the CD4 counts have increased.
   C. Continue maintenance therapy with fluconazole until CD4 counts are greater than 500 cells/mm^3.
   D. Discontinue maintenance therapy with fluconazole.

6. Signs and symptoms
   a. Almost always meningitis (66%–84%)
   b. Usually present for weeks or months (1 day to 4 months; average, 31 days)
   c. Insidious onset
      i. Low-grade fever (80%–90%)
      ii. Headaches (80%–90%)
      iii. Altered sensorium (20%): Irritability, somnolence, clumsiness, impaired memory and judgment, behavioral changes
      iv. Seizures may occur late in the course (less than 10%).
      v. Minimal nuchal rigidity, meningismus, photophobia
7. Diagnosis
   a. Cerebrospinal fluid (CSF) changes including:
      i. Positive CSF cultures
      ii. CSF cryptococcal antigen titer (91%)
      iii. Elevated opening pressure greater than 20 cm H_2O
   b. Serum cryptococcal antigen more than 1:8
8. Induction therapy (at least 2 weeks)
   a. Preferred:
      i. Liposomal amphotericin B 3–4 mg/kg/day plus flucytosine 25 mg/kg every 6 hours
      ii. Amphotericin B deoxycholate 0.7–1 mg/kg/day plus flucytosine 25 mg/kg every 6 hours (only if cost is an issue and the risk of renal dysfunction is low)

b. Alternatives:
   i. Amphotericin B lipid complex 5 mg/kg/day plus flucytosine 25 mg/kg every 6 hours
   ii. Liposomal amphotericin B 3–4 mg/kg/day plus fluconazole 800 mg/day
   iii. Amphotericin B deoxycholate 0.7–1 mg/kg/day plus fluconazole 800 mg/day
   iv. Liposomal amphotericin B 3–4 mg/kg/day
   v. Fluconazole 400–800 mg/day plus flucytosine 25 mg/kg every 6 hours
   vi. Fluconazole 1200 mg/day alone

9. Consolidation therapy (at least 8 weeks, beginning after successful induction therapy [negative CSF culture])
   a. Fluconazole 400 mg daily
   b. Alternative: Itraconazole 200 mg twice daily (less effective than fluconazole)
10. Maintenance therapy – Preferred: Fluconazole 200 mg/day for at least 1 year
11. Outcome
   a. Delay initiating combination ART in patients with cryptococcal meningitis for 2–10 weeks because of the risk of IRIS.
   b. Therapeutic response: 42%–75%
   c. Relapse: 50%–90% (with about 100% mortality)
12. Prophylaxis
   a. Relapses usually occur within first year after therapy (less often with potent combination ART).
   b. Secondary prophylaxis: Fluconazole 200 mg/day (may consider discontinuing after a minimum of 1 year of chronic maintenance therapy if CD4 count is more than 100 cells/mm^3 for 3 months or longer after potent combination ART and patient remains asymptomatic; reinitiate if CD4 count decreases to less than 100 cells/mm^3)
   c. Primary prophylaxis: Not indicated (decreases the incidence of cryptococcosis but does not decrease mortality and may lead to resistance)

Patient Case

7. J.C. is a 36-year-old HIV-positive woman with severe anemia. She has been tested for iron deficiency and has been taken off zidovudine and trimethoprim/sulfamethoxazole. She has also started to lose weight and to have severe diarrhea. A blood culture is positive for MAI. Which treatment is best for J.C.?

   A. Clarithromycin plus ethambutol for 2 weeks, followed by maintenance with clarithromycin alone.

   B. Azithromycin plus ethambutol for at least 12 months.

   C. Clarithromycin plus isoniazid for 2 weeks, followed by maintenance with clarithromycin alone.

   D. Ethambutol plus rifabutin indefinitely.

F. *M. avium* Complex
   1. Organism characteristics
      a. Complex is similar (main species are *M. avium* and *Mycobacterium intracellulare,* which are not differentiated microbiologically).
      b. Ubiquitous in soil and water and are transmitted through inhalation, ingestion, or inoculation by the respiratory or gastrointestinal (GI) tract
      c. Usually occurs in patients with HIV having a CD4 count less than 50 cells/mm^3
      d. MAC is independently associated with risk of death, and treatment prolongs survival.
   2. Signs and symptoms (nonspecific)
      a. Weight loss, intermittent fevers, chills, night sweats, abdominal pain, diarrhea, chronic malabsorption, and progressive weakness
      b. Anemia
      c. Elevated alkaline phosphatase

3. Diagnosis
    a. Blood or lymph node culture
    b. Bone marrow biopsy
    c. Stool cultures (do not treat if cultured only in the stool)
4. Therapy
    a. Preferred therapeutic regimen is macrolide plus ethambutol: Clarithromycin 500 mg (7.5–15 mg/kg) twice daily *or* azithromycin 500–600 mg/day (10–20 mg/kg) if drug interactions or intolerance to clarithromycin, plus ethambutol 15 mg/kg/day for 12 months
    b. Other agents: Consider adding to preferred therapy if advanced immunosuppression (CD4 count less than 50 cells/mm^3), high mycobacterial loads (more than 2 log CFU/mL of blood), or in the absence of effective ART.
        i. Rifabutin (Mycobutin) 300 mg/day (rifabutin dose chosen on the basis of other antiretrovirals because of drug-drug interactions)
        ii. A fluoroquinolone such as levofloxacin 500 mg oral daily or moxifloxacin 400 mg oral daily
        iii. An aminoglycoside such as amikacin 10–15 mg/kg intravenously daily or streptomycin 1 g intravenously or intramuscularly daily
    c. Chronic maintenance therapy or secondary prophylaxis may be discontinued after 12 months of therapy if CD4 count is more than 100 cells/mm^3 for 6 months or longer because of potent combination ART and if patient is asymptomatic. Restart if CD4 count drops below 100 cells/mm^3.
5. Primary prophylaxis in patients with CD4 counts less than 50 cells/mm^3 who are not receiving ART or who have viremia on current ART (may be discontinued upon initiation of effective ART); primary prophylaxis not recommended if patients are immediately initiated on ART
    a. Clarithromycin 500 mg orally twice daily: Lower incidence of MAC bacteremia (vs. placebo)
    b. Azithromycin 1200 mg orally once weekly
    c. Azithromycin 600 mg orally twice weekly
    d. Alternative: Rifabutin 300 mg/day (150 mg orally twice daily with food if there are GI adverse effects)

G. Cytomegalovirus
1. Characteristics of CMV infection
    a. Fifty-three percent of Americans age 18–25 years are CMV positive.
    b. Eighty-one percent of Americans older than 35 years are CMV positive.
    c. More than 95% of men who have sex with men are CMV positive.
    d. About 90% of CMV infections are asymptomatic (if illness occurs, it resembles mononucleosis).
    e. Virus remains latent in the host after initial infection but may reactivate if patient becomes immunocompromised (especially cell-mediated immunity).
2. Diagnosis of CMV infection: Usually made on the basis of clinical manifestations
3. Manifestations of CMV
    a. Retinitis
        i. Occurs in 10%–15% of patients with AIDS; is clinically most important CMV infection
        ii. In general, patients have CD4 counts less than 50 cells/mm^3 and high plasma HIV RNA concentrations.
        iii. Begins unilaterally and spreads bilaterally
        iv. Early complaints: "Floaters," pain behind the eye
        v. In general, progressive; no spontaneous resolution (blindness in weeks to months)
        vi. Twenty-six percent progression, even with treatment; retinal detachment very common
    b. Other manifestations
        i. Esophagitis or colitis
        ii. Pneumonitis
        iii. Neurologic

4. Therapy for CMV infections
    a. CMV retinitis
        i. Sight-threatening lesions
            (a) Valganciclovir 900 mg orally twice daily for 14–21 days, followed by 900 mg orally daily, plus intravitreal injections of ganciclovir or foscarnet for 1–4 doses over a period of 7–10 days
            (b) Alternative therapy (all regimens include intravitreal injections as listed above):
                (1) Ganciclovir 5 mg/kg intravenously every 12 hours for 14–21 days, followed by ganciclovir 5 mg/kg intravenously daily or valganciclovir 900 mg orally daily
                (2) Foscarnet 60 mg/kg intravenously every 8 hours or 90 mg/kg intravenously every 12 hours for 14–21 days, then 90–120 mg/kg intravenously daily
                (3) Cidofovir 5 mg/kg weekly intravenously for 2 weeks; then 5 mg/kg every other week with saline hydration and probenecid
        ii. Peripheral lesions
            (a) Valganciclovir 900 mg orally twice daily for 14–21 days, followed by 900 mg orally daily.
            (b) Alternative therapy:
                (1) Ganciclovir 5 mg/kg intravenously 5–7 times weekly
                (2) Foscarnet 90–120 mg/kg intravenously daily
                (3) Cidofovir 5 mg/kg every other week intravenously with saline hydration and probenecid
    b. Other CMV infections
        i. Esophagitis or colitis
            (a) Ganciclovir 5 mg/kg intravenously every 12 hours, followed by valganciclovir 900 mg orally twice daily when tolerated
            (b) Alternative therapy:
                (1) Foscarnet 60 mg/kg intravenously every 8 hours or 90 mg/kg intravenously every 12 hours
                (2) Valganciclovir 900 mg orally twice daily (if tolerable)
        ii. Pneumonitis – Use ganciclovir or foscarnet at retinitis doses.
        iii. Neurologic – Combination of ganciclovir and foscarnet at retinitis doses
5. Consider waiting up to 2 weeks after initiating CMV therapy to start ART in a treatment-naive patient
6. Prophylaxis
    a. Secondary prophylaxis is necessary for all patients (see individual drugs for specific doses); it may be discontinued if the CD4 count is more than 100 cells/mm^3 for 3–6 months or longer because of potent combination ART and signs/symptoms (including active lesions) have resolved. Reinitiate secondary prophylaxis if the CD4 count decreases to less than 100 cells/mm^3.
    b. Primary prophylaxis not recommended. In patients with CD4 counts less than 50 cells/mm^3, regular funduscopic examinations are recommended.

III. TUBERCULOSIS

A. *Mycobacterium tuberculosis*
1. Factors associated with acquiring TB
    a. Exposure to people with active pulmonary TB
    b. Geographic location
    c. Low socioeconomic status
    d. Nonwhite race
    e. Male sex
    f. HIV infection
    g. Foreign birth

2. Epidemiology (Figure 2)

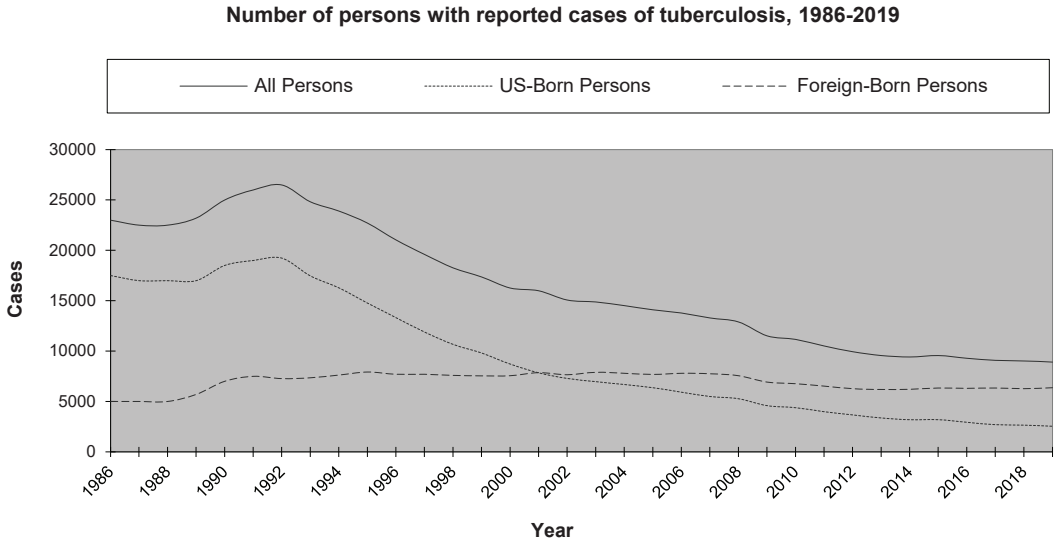

Figure 2. Epidemiology of tuberculosis.

B. Pathophysiology (Figure 3)
   1. Person-to-person transmission: Airborne droplets carrying *M. tuberculosis* are inhaled.
   2. Infection primarily pulmonary but can occur in other organ systems

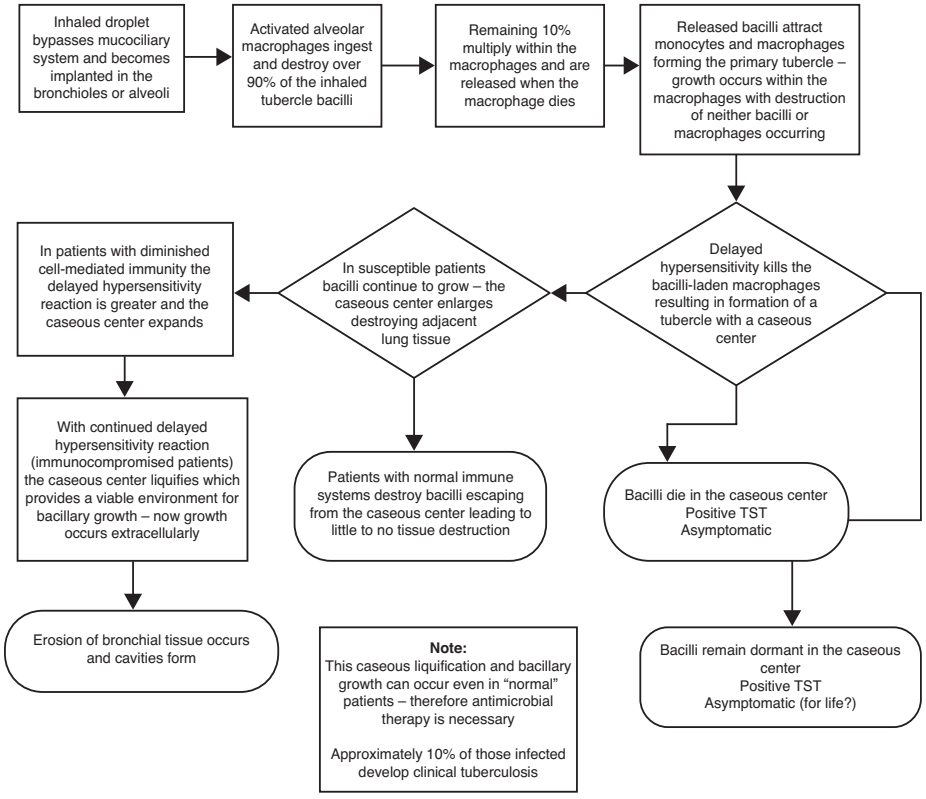
Inhaled droplet bypasses mucociliary system and becomes implanted in the bronchioles or alveoli
Activated alveolar macrophages ingest and destroy over 90% of the inhaled tubercle bacilli
Remaining 10% multiply within the macrophages and are released when the macrophage dies
Released bacilli attract monocytes and macrophages forming the primary tubercle – growth occurs within the macrophages with destruction of neither bacilli or macrophages occurring
Delayed hypersensitivity kills the bacilli-laden macrophages resulting in formation of a tubercle with a caseous center
In susceptible patients bacilli continue to grow – the caseous center enlarges destroying adjacent lung tissue
In patients with diminished cell-mediated immunity the delayed hypersensitivity reaction is greater and the caseous center expands
With continued delayed hypersensitivity reaction (immunocompromised patients) the caseous center liquifies which provides a viable environment for bacillary growth – now growth occurs extracellularly
Erosion of bronchial tissue occurs and cavities form
Patients with normal immune systems destroy bacilli escaping from the caseous center leading to little to no tissue destruction
Bacilli die in the caseous center
Positive TST
Asymptomatic
Bacilli remain dormant in the caseous center
Positive TST
Asymptomatic (for life?)
Note:
This caseous liquification and bacillary growth can occur even in "normal" patients – therefore antimicrobial therapy is necessary
Approximately 10% of those infected develop clinical tuberculosis

Figure 3. Pathophysiology of tuberculosis.
TST = tuberculin skin test

C. Diagnosis (Table 8)

Table 8. Diagnosis of Tuberculosis

Nonspecific Signs and Symptoms	Radiology	Microbiology
Cough Malaise Weight loss Fever, chills Night sweats Pleuritic pain	Chest radiograph: patchy or nodular infiltrates in upper lobes; cavitary lesions	Sputum smear for AFB Sputum culture for *Mycobacterium tuberculosis* Rapid detection through PCR probe

AFB = acid-fast bacillus; PCR = polymerase chain reaction.

1. Tuberculin skin test (TST) (Table 9)
   a. Recommended dose is 5 tuberculin units/0.1 mL.
   b. Mantoux method
      i. Intradermal injection of tuberculin into forearm
      ii. Measure diameter of induration after 48–72 hours.
   c. False-negative tests occur in 15%–20% of people infected with *M. tuberculosis,* primarily in those recently infected or anergic.
   d. Only 8% of people vaccinated with bacille Calmette-Guérin (BCG) at birth will react 15 years later.

Table 9. Testing for Latent Tuberculosis Infection

Likelihood of Infection with M. tuberculosis (see below)	Risk of Progressing to Tuberculosis if Infected (see below)	Criterion for Positive Skin Test (mm)	Recommended testing*
Likely	Low to intermediate	≥ 10	IGRA recommended if history of BCG vaccine or unlikely to return to have TST read (otherwise IGRA suggested) TST is acceptable alternative
Likely	High	≥ 5	IGRA or TST (data insufficient to recommend one over the other)
Unlikely	Low to high	≥ 15	Do not test with either IGRA or TST (may be done for employee health surveillance)

Groups with increased likelihood to be infected (i.e., "likely") • Household contact or recent exposure of an active case • Mycobacteriology laboratory personnel • Immigrants from high-burden countries • Residents and employees of high-risk congregate settings	**Risk of Developing Tuberculosis** Low: • No risk factors Intermediate: • Diabetes • Chronic renal failure • Intravenous drug use High: • Children < 5 years • HIV infection • Immunosuppressive therapy • Abnormal chest x-ray consistent with prior TB • Silicosis

* For children under 5 years of age use TST rather than an IGRA in all situations

2. Interferon-gamma release assays (IGRA)
    a. QuantiFERON-TB Gold and T-SPOT.TB
    b. Blood test that detects the release of interferon gamma in response to *M. tuberculosis* infection
    c. Less sensitivity but greater specificity than the TST for predicting future active infection
3. Booster effect
    a. The TB test can restimulate hypersensitivity in those exposed in the past.
    b. Occurs within 1 week of the test and persists for more than 1 year
    c. Those with small TB test reactions can be retested in 1 week; if positive, result should be attributed to boosting of a subclinical hypersensitivity; chemoprophylaxis is not necessary.

Patient Case

8. J.M. is a 42-year-old man who works at a long-term care facility and was recently exposed to a patient with TB. A TST is placed, and 48 hours later, he has an 18-mm induration. This is the first time he has reacted to this test. His chest radiograph is negative. Which is best in view of J.M.'s positive TST?

    A. No treatment is necessary, and J.M. should have another TST skin test in 1 year.

    B. J.M. should have another TST skin test in 1 week to see whether this is a booster effect.

    C. J.M. should be monitored closely, but no treatment is necessary because he is older than 35 years.

    D. J.M. should be initiated on isoniazid 300 mg/day orally for 9 months.

D. Therapy
    1. Treatment of latent TB infection
        a. The goal is to prevent latent (asymptomatic) infection from progressing to clinical disease.
        b. Treatment of latent TB infection is recommended for the following people:
            i. HIV infected persons
            ii. Close contacts of people with a diagnosed infectious TB
            iii. People with abnormal chest radiographs that show fibrotic lesions, likely to represent old, healed TB
            iv. Immunosuppressed persons (e.g., organ transplant recipients, taking the equivalent of more than 15 mg/day of prednisone for more than 1 month, receiving TNF-alpha antagonists)
            v. Foreign-born people from high-prevalence countries (immigration within 5 years)
            vi. PWID (people who inject drugs)
            vii. People working at or living in high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospital, and other health care facilities)
            viii. Mycobacteriology laboratory personnel
            ix. Children under 4 years of age, or children and adolescents exposed to adults in high-risk categories
        c. Dosing regimens
            i. Patients who are not infected with HIV
                (a) Rifapentine 900 mg plus isoniazid 900 mg/week for 12 weeks (with directly observed therapy)
                (b) Rifampin 600 mg/day for 4 months
                (c) Rifampin 600 mg/day plus isoniazid 300 mg/day for 3 months
                (d) Isoniazid 300 mg/day or 900 mg twice weekly for 6–9 months (9 months preferred, especially for children and pregnant women)

ii. Patients who are coinfected with HIV
   (a) Isoniazid 300 mg/day for 9 months
   (b) Alternative: Rifapentine 750–900 mg plus isoniazid 900 mg/week for 12 weeks (only for patients receiving raltegravir or efavirenz ART); rifampin 600 mg/day for 4 months (use only when isoniazid cannot be given, and watch drug interactions)

iii. Areas with multidrug-resistant isolates: Two drugs with activity against the isolate for 6–12 months

Patient Case

9. R.J. is a 32-year-old HIV-positive man who presents to the clinic with increased weight loss, night sweats, and a cough productive of sputum. He is currently receiving darunavir/ritonavir 800 mg/100 mg daily, tenofovir 300 mg daily, emtricitabine 200 mg daily, fluconazole 200 mg/day orally, and trimethoprim/sulfamethoxazole double strength daily. A sputum sample is positive for acid-fast bacillus. R.J. lives in an area with a low incidence of multidrug-resistant TB. Which is the best initial treatment?

   A. Initiate isoniazid, rifampin, and pyrazinamide with no change in HIV medications.

   B. Initiate isoniazid, rifampin, and pyrazinamide; increase the dosage of darunavir/ritonavir; and use a higher dosage of rifamycin.

   C. Initiate isoniazid, rifabutin, pyrazinamide, and ethambutol, with a lower dosage of rifabutin.

   D. Initiate isoniazid, rifabutin, pyrazinamide, and ethambutol, and decrease the dosage of darunavir/ritonavir.

2. Treatment of active TB infection (Tables 10 and 11)
   a. Principles of treatment
      i. Regimens must contain many drugs to which the organisms are susceptible.
      ii. Drug therapy must continue for a sufficient period.

Table 10. Pharmacotherapeutic Agents in the Treatment of Tuberculosis

First-Line Agents	Second-Line Agents
Isoniazid	Amikacin/kanamycin
Rifampin	Bedaquiline
Pyrazinamide	Capreomycin
Ethambutol	Cycloserine
	Ethionamide
	Fluoroquinolones
	Para-aminosalicylic acid
	Pretomanid
	Rifabutin
	Rifapentine
	Streptomycin

   b. Therapeutic options for treating active TB (Note: Any regimen administered two, three, or five times/week should be done by directly observed therapy.)

Table 11. Treatment of Tuberculosis

	Patients without HIV		Patients with HIV	
Recommended	**Antibiotic**	**Regimen**	**Antibiotic**	**Regimen**
Intensive Phase[a]	Isoniazid[b] Rifampin Pyrazinamide Ethambutol	Treat for 2 months (daily or five times weekly)	Isoniazid Rifamycin Pyrazinamide Ethambutol	Treat for 2 months (daily or five times weekly)
Continuation Phase	Isoniazid Rifampin	Treat for 4 months[c] (daily or five times weekly)	Isoniazid Rifamycin	Treat for 4 months[d] (daily or five times weekly)
Optional (less efficacy)[e]	**Antibiotic**	**Regimen**	**Antibiotic**	**Regimen**
Intensive Phase[a]	Isoniazid Rifampin Pyrazinamide Ethambutol	Treat for 2 months (three times weekly or daily for two weeks followed by two times weekly)	N/A	N/A
Continuation Phase	Isoniazid Rifampin	Treat for 4 months (three times weekly or twice weekly)	N/A	N/A

[a]If TB isolate is susceptible to both INH and RIF, then ethambutol can be dropped from the intensive phase.

[b]Pyridoxine should be given to all those receiving isoniazid and at increased risk of neuropathy (e.g., pregnant women, breastfeeding infants, HIV infected persons, patients with diabetes, alcoholism, malnutrition, or chronic renal failure, persons of advanced age).

[c]Extend to 7 months if cavitary lesions on chest x-ray and positive sputum culture after intensive phase.

[d]Extend to 7 months if patient not receiving ART.

[e]Efficacy diminishes as the number of weekly doses decreases.

c. Concurrent therapy in patients with HIV
   i. For ART-naive patients, ART should be initiated within 2 weeks when the CD4 count is less than 50 cells/mm^3 and by 8–12 weeks for all others.
   ii. PIs and NNRTIs (except for efavirenz or nevirapine) should not be administered concurrently with rifampin; INSTIs can be administered with rifampin (except elvitegravir and bictegravir), but doses need to be altered; NRTIs can be administered with rifampin, except for tenofovir alafenamide (which should not be administered with any rifamycin).
   iii. A washout period of 1–2 weeks may be necessary once rifampin is discontinued before PIs, elvitegravir, or NNRTIs are initiated.
   iv. Rifabutin can be substituted for rifampin; patients may take NNRTIs with rifabutin, but rifabutin doses may need to be increased to 450–600 mg/day (see HIV guidelines).
   v. Patients may take PIs with rifabutin, but the rifabutin dose should be decreased to 150 mg every day or every other day (300 mg three times weekly may be an option).
   vi. Elvitegravir and bictegravir should not be used with rifabutin.
   vii. Patients taking rifabutin and PIs, INSTIs, or NNRTIs should have HIV RNA and rifabutin concentrations performed periodically.
   viii. Rifapentine should only be given to patients receiving either an efavirenz- or raltegravir-based regimen.

d. Known drug resistance to isoniazid: Administer rifampin, pyrazinamide, ethambutol, and moxifloxacin or levofloxacin for 2 months; rifabutin may be substituted for rifampin in patients with HIV. Continuation phase should be completed with rifampin (or rifabutin) plus ethambutol plus moxifloxacin (or levofloxacin) for 7 months.

e. Known drug resistance to rifampin: Administer isoniazid, pyrazinamide, and ethambutol for 9–12 months; streptomycin may be added for the first 2 months to shorten the total treatment time to 9 months.

f. Total duration of therapy should be based on number of doses received, not on calendar time.
   i. Pulmonary TB: 6 months
   ii. Pulmonary TB and culture positive after 2 months of TB treatment: 9 months
   iii. Extrapulmonary TB with central nervous system (CNS) infection: 9–12 months
   iv. Extrapulmonary TB with bone or joint involvement: 6–9 months
   v. Extrapulmonary TB in other sites: 6 months

Patient Cases

10. Which represents the best follow-up for R.J. (from Patient Case 9)?
    A. Treatment with the initial drugs should continue for 6 months.
    B. Treatment can be decreased to just isoniazid and a rifamycin after 2 months for a total treatment of 18–24 months.
    C. Treatment can be decreased to just isoniazid and a rifamycin after 2 months for a total treatment of 6 months; HIV RNA concentrations should be observed closely during therapy.
    D. Treatment can be decreased to isoniazid, a rifamycin, and either pyrazinamide or ethambutol after 2 months for a total treatment of 6 months; HIV RNA concentrations should be observed closely during therapy.

11. L.F. is a 55-year-old man (73 kg) who was involved in a motor vehicle accident with subsequent bilateral pneumothoraces. He is admitted to the ICU and mechanically ventilated. He is started on levofloxacin which after 3 days is switched to piperacillin/tazobactam and vancomycin. After 5 days of broad spectrum antibiotics his temperature continues to spike. A blood culture is positive for *Candida krusei*. What is the best treatment for L.F.?
    A. Fluconazole 400 mg IV daily for 7 days following the first negative blood culture.
    B. Micafungin 100 mg IV daily for 14 days following the first negative blood culture.
    C. Amphotericin B lipid formulation 3 mg/kg/day for 14 days following the first negative blood culture.
    D. Voriconazole 200 mg IV twice daily for 7 days following the first negative blood culture.

IV. FUNGAL PHARMACOTHERAPY

A. Candida
   1. Background
      a. *C. albicans*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. auris*
      b. Risk factors:
         i. Broad spectrum antibiotics
         ii. Central catheters, urinary catheters, etc. (remove if found to be the source of infection)
         iii. Prosthetic devices
         iv. Immunocompromised (chemotherapy, radiation, corticosteroid, HIV, etc.)
   2. Therapy
      a. Oral/esophageal candidiasis (see II. Opportunistic Infections: Patients With HIV, C. Candida Infections)
      b. Candidemia
         i. Echinocandin (caspofungin, anidulafungin, or micafungin)
         ii. Fluconazole: only use if known or suspected fluconazole-sensitive organism (400 mg/day)
         iii. Amphotericin B lipid formulation – for resistance or intolerance to other antifungals
         iv. Treat for 14 days after first negative blood culture

c. Endocarditis
    i. Amphotericin B lipid formulation ± flucytosine or high dose echinocandin
    ii. Fluconazole (or voriconazole or posaconazole) can be used as step down therapy for sensitive isolates
    iii. Replace the valve and treat for 6 weeks
    iv. Consider chronic suppressive therapy with fluconazole for prosthetic valve endocarditis
d. Osteomyelitis/Septic arthritis
    i. Fluconazole for 6-12 months
    ii. Echinocandin for 2 weeks followed by fluconazole for 6-12 months
    iii. Amphotericin B lipid formulation for 2 weeks followed by fluconazole for 6-12 months
    iv. Same recommendations for septic arthritis except total therapy is only 6 weeks
e. Urinary tract infections
    i. Remove indwelling catheters, nephrostomy tubes, stents, etc.
    ii. Asymptomatic: treat only if patient is neutropenic or undergoing urologic manipulation
    iii. Symptomatic
        (a) Fluconazole for 2 weeks
        (b) Amphotericin B deoxycholate (not liposomal preparations) (1-7 days) or flucytosine (7-10 days) for fluconazole resistant organisms
        (c) Other azoles and echinocandins do not achieve adequate urinary concentrations
f. Invasive Candidiasis in the Intensive Care Unit
    i. Empiric treatment
        (a) Use for patients with unexplained fever and risk factors: *Candida* colonization, severe illness, broad spectrum antibiotics, recent abdominal surgery, necrotizing pancreatitis, dialysis, parenteral nutrition, corticosteroids, central venous catheter
        (b) Echinocandin therapy recommended
        (c) Fluconazole use only in patients without recent azole use or colonization with azole-resistant organisms
        (d) Amphotericin B lipid formulation if patient intolerant to other antifungals
        (e) Duration: 2 weeks if patient responds or 4-5 days with no response
    ii. Prophylaxis
        (a) Fluconazole 400 mg daily in ICUs where invasive candidiasis occurs in more than 5% of patients
        (b) Echinocandins can be used alternatively

B. Histoplasmosis
1. Background
    a. *Histoplasma capsulatum*
    b. Endemic regions: lower Mississippi and Ohio valleys
    c. Organisms in excrement are aerosolized and inhaled
    d. Signs and symptoms: lymphadenopathy, splenomegaly, fever, weight loss, headache, chills, cough, chest pain, myalgias, fatigue
2. Therapy
    a. 50% mortality even with therapy – relapses are frequent
    b. Moderate to severe illness: Lipid formulation amphotericin B (3–5 mg/kg/day) for at least 1-2 weeks followed by itraconazole to complete 12 weeks of therapy
    c. Mild illness: itraconazole 200 mg three times daily for 3 days and then twice daily for 12 weeks (may need to extend to 12-24 months in patients with chronic or disseminated disease)

C. Coccidioidomycosis
   1. Background
      a. *Coccidioides immitis*
      b. Endemic regions: California, Arizona, Nevada, New Mexico, Utah, Texas
      c. Organisms in soil are aerosolized and inhaled
      d. Signs and symptoms: cough, sputum production, chest pain, malaise, fever, chills, night sweats, anorexia, weakness, arthralgias
   2. Therapy
      a. Consider not treating in immunocompetent host
      b. Fluconazole 400 mg daily or itraconazole 400 mg/day for 3-6 months
      c. Severe/diffuse/disseminated disease: amphotericin B lipid formulation (5 mg/kg/day) until improvement then fluconazole or itraconazole for at least a year

D. Blastomycosis
   1. Background
      a. *Blastomyces dermatitidis*
      b. Endemic regions: Southeastern states, Ohio and Mississippi river basins, and Great Lakes region including the St. Lawrence seaway
      c. Sources: soil – organisms in soil are aerosolized and inhaled
      d. Signs and symptoms: cough, sputum production, chest pain, malaise, fever, chills, weakness, arthralgias
      e. Cutaneous manifestations (occurs in 40-80% of patients): small papulopustular lesions that spread to form a crusted, heaped-up lesion or an ulcerative pustular lesion
   2. Therapy
      a. Itraconazole 200 mg three times daily for 3 days and then twice daily for 24 weeks
      b. Severe/life threatening disease: amphotericin B lipid formulation (5 mg/kg/day) until improvement then itraconazole for 6-12 months

E. Aspergillosis
   1. Background
      a. *Aspergillus fumigatus*
      b. Ubiquitous in the environment
      c. Sources: grows in stored hay/grain, decaying vegetation, soil, compost piles, and manure – common during hospital renovation / construction, in potted plants, and air conditioner filters – organisms are aerosolized and inhaled
      d. Allergic bronchopulmonary aspergillosis – in asthma patients, aspergillosis causes hypersensitivity reaction and granuloma formation (treat with prednisone)
      e. Pneumonia – secondary to prolonged neutropenia; high fever and dense pulmonary infiltrates – rapidly progressing and universally fatal in bone marrow transplant patients
   2. Therapy
      a. Voriconazole 6 mg/kg twice daily for two doses and then 4 mg/kg intravenously twice daily or 200-300 mg orally twice daily
      b. Alternatives: isavuconazole 200 mg every 8 hours for six doses and then 200 mg daily or amphotericin B lipid formulation (3-5 mg/kg/day)
      c. Echinocandins only if azoles and amphotericin are contraindicated
      d. Treat for 6-12 weeks
   3. Prophylaxis
      a. Recommended for at-risk patients with prolonged neutropenia, graft versus host disease or lung transplant
      b. Voriconazole or posaconazole or micafungin (use voriconazole, itraconazole, or inhaled amphotericin for 3-4 months after lung transplant)

F. Mucormycosis
   1. Background
      a. *Rhizopus* spp. and *Mucor* spp.
      b. Ubiquitous in the environment
      c. Sources: decaying organic matter – organisms are aerosolized and inhaled
      d. Signs and symptoms: fever, cough, shortness of breath (pulmonary); can also cause sinusitis with associated symptoms or cutaneous infections
   2. Therapy
      a. Amphotericin B lipid formulation (5 mg/kg/day) until improvement then isavuconazole or posaconazole
      b. Treat until resolution of infection (usually months)

Patient Case

12. A.B. is a 55-year-old woman who presents to your clinic with toenail discoloration with a few of her toenails separating from the nail bed. She is diagnosed with onychomycosis. What is the best treatment for A.B.?
    A. Fluconazole 200 mg orally daily for 14 days.
    B. Itraconazole 200 mg orally daily for 28 days.
    C. Miconazole cream applied twice daily to toenails for 2 months.
    D. Terbinafine 250 mg orally daily for 3 months.

G. Superficial fungal infections
   1. Background
      a. Caused by dermatophytes (*Microsporum*, *Trichophyton*, *Epidermophyton*)
      b. More common in males than females
      c. More common in tropical, humid climates
      d. Transmitted person to person, via soil contact and via animal contact
   2. Tinea capitis – infection of the scalp
      a. Peak incidence of 3-9 years of age, more common in nonwhites
      b. Spores invade the hair shaft leading to hair loss without inflammation or spores spread beyond the hair shaft leading to inflammation
      c. Therapy:
         i. Griseofulvin (preferable for *Microsporum*) 10–15 mg/kg/day for 6–8 weeks
         ii. Terbinafine (preferable for *Trichophyton*): Weight less than 10 kg: 62.5 mg; 10–20 kg: 125 mg; greater than 20 kg: 250 mg daily for 4 weeks
         iii. Itraconazole, fluconazole – alternatives; treat for 4–6 weeks
         iv. Selenium sulfide 2.5% shampoo (reduces spread of infection and reinfection)
   3. Tinea pedis – infection of the foot
      a. Increase in frequency with age; more common in men than women, and in those who wear shoes
      b. Moccasin like distribution (difficult to treat) or intertrigenous involvement which may lead to secondary bacterial infection
      c. Therapy:
         i. Topical antifungal agent twice daily until clear
         ii. Terbinafine, itraconazole, or fluconazole for severe or resistant cases
   4. Tinea cruris – infection of the groin and thigh
      a. More common in males than females
      b. Predisposing factors include obesity, tight-fitting clothes, wet swimsuits, etc.
      c. Therapy:
         i. Topical antifungals twice daily for 3-4 weeks
         ii. Loose-fitting cotton underwear and good hygiene

5. Tinea corporis – "ringworm"
    a. Common in hot, humid climates – transmitted person to person
    b. Asymptomatic or pruritic annular plaque – scaling, crusting, vesicle formation and papules on nonhairy skin
    c. Therapy:
        i. Topical antifungal twice daily for 2-4 weeks
        ii. Terbinafine or itraconazole for extensive skin involvement
6. Onychomycosis – nail infection
    a. Increases with age – affects 5% of the population
    b. Predisposing factors include superficial fungal infection of feet or hands, repeated minor trauma with heat and moisture
    c. Nail discoloration, subungual hyperkeratosis, separation of nail from bed
    d. Therapy:
        i. Terbinafine
        ii. Itraconazole (pulse or continuous therapy)
        iii. Onychomycosis specific topical agents: efinaconazole, tavaborole, or ciclopirox
        iv. Duration: fingernails: 6 weeks; toenails: 12 weeks (longer if using topical agents)

Patient Case

13. C.A. is a 66-year-old man with a history of advanced non–small cell lung cancer. After his most recent chemotherapy, he became severely neutropenic and received a diagnosis of *Aspergillus* pneumonia. C.A. has acute renal failure related to his chemotherapy and is receiving warfarin, diltiazem, dronedarone, atorvastatin, pantoprazole, and carbamazepine. Which antifungal would be the best therapy for C.A.?

    A. Lipid amphotericin.

    B. Micafungin.

    C. Fluconazole.

    D. Voriconazole.

V. ANTIFUNGAL AGENTS

A. Amphotericin B (Fungizone, Abelcet, Amphotec, AmBisome)
    1. Mechanism of action: Binds to ergosterol in the fungal cell membrane, altering membrane permeability and causing cell lysis
    2. Spectrum of activity
        a. *Candida, Blastomyces dermatitidis, Coccidioides immitis, C. neoformans, Paracoccidioides, Histoplasma capsulatum, Sporothrix, Aspergillus,* mucormycoses
        b. Clinical use
            i. Cryptococcal meningitis
            ii. Systemic fungal infections caused by sensitive fungi
            iii. Limited use clinically with newer antifungals
    3. Adverse effects (less common with lipid formulations)
        a. Renal toxicity (glomerular and tubular)
            i. Glomerular filtration rate decreases by about 40% within 2 weeks and usually stabilizes at 20%–60% of normal.
            ii. In general, reversible unless total dose is more than 4–5 g
            iii. Manifestations: Renal tubular acidosis, urine casts, azotemia, oliguria, magnesium, and potassium wasting

iv. Prevention
(a) Correct salt depletion: 3 L normal saline for 24 hours or 500 mL of normal saline before and after amphotericin dose
(b) Avoid diuretics and liberalize salt intake; risk-benefit with other disease states

b. Thrombophlebitis prevention (deoxycholate formulation only)
i. Dilute to 0.1 mg/mL and infuse for at least 4 hours; a faster infusion (i.e., 45 minutes to 2 hours) may be tolerated.
ii. Use a central site.
iii. Adding heparin may decrease phlebitis.

c. Anemia

d. Fever and chills
i. Mechanism: Amphotericin B induces prostaglandin synthesis.
ii. Premedications
(a) Hydrocortisone: 25 mg intravenously before the dose or in the bottle decreases fever and chills (higher doses are not significantly better)
(b) Ibuprofen (10 mg/kg up to 600 mg 30 minutes before infusion): Significantly more fever and chills in placebo (87%) than in ibuprofen group (48%)
(c) Acetylsalicylic acid, acetaminophen, diphenhydramine: Never shown to be effective (but not specifically studied)

e. Rigors treatment
i. Meperidine 50 mg: Stops reaction within 30 minutes (mean, 10.8 minutes)
ii. If the patient consistently needs meperidine, then prophylactic doses may be appropriate.

4. Dosing
a. Start therapy with 0.25 mg/kg (some suggest 5–10 mg) administered for 4–6 hours.
b. Increase gradually to desired milligram per kilogram concentration (i.e., 5- to 10-mg increments).
c. May increase rapidly in fulminant infections or immunocompromised patients
d. Amphotericin can be given on alternate days by doubling the daily dose to a maximum of 1.5 mg/kg.

5. Lipid amphotericin formulations (liposome, lipid complex, and colloidal dispersion; Table 12)
a. Lipid formulations are designed to maintain therapeutic efficacy, but they diminish renal and infusion-related toxicity.
b. Mainly taken up by macrophages in the lung, liver, spleen, bone marrow, and circulating monocytes
c. Liposomes target fungal cell membranes much more than human cell membranes.
d. Amphotericin dissociates from the liposome over time, decreasing its toxicity (only free drug is toxic).
e. Primary use in patients with aspergillosis and cryptococcal meningitis who cannot tolerate amphotericin B deoxycholate
f. Potential use for invasive candidiasis

B. Azole Antifungals
1. Mechanism of action: Inhibits the synthesis of ergosterol, a component of the fungal cell membrane, vital for normal growth
2. Fluconazole (Diflucan)
a. Spectrum of activity
i. *Candida* spp. (poor activity against *C. glabrata* and no activity against *C. krusei*), *Cryptococcus, Blastomyces, Histoplasma,* dermatophytes
ii. Clinical use
(a) *Candida* infections (primarily *C. albicans* and *C. parapsilosis*)
(b) Cryptococcal meningitis

Table 12. Amphotericin Formulations

	Amphotericin B Deoxycholate	Abelcet	Amphotec	AmBisome
Lipid type		Multilamellar vesicle with ribbonlike structure (lipid complex)	Colloidal dispersion in aqueous solution (disk-shaped bilayer)	Unilamellar liposome
Dose	0.7–1 mg/kg/day	5 mg/kg/day for 2 hours	3–4 mg/kg/day for 3–4 hours	3–5 mg/kg/day
Test dose	Yes	None	Yes	None
Chills or rigors (%)	54–56	18	77	18
Fever (%)	44–47	14	55	17
Nephrotoxicity (%)	34–47	28	8	19
Hypokalemia (%)	12–29	5	26	7
Hypomagnesemia (%)	11–26	N/A	6	20

b. Pharmacokinetics
   i. Well absorbed orally (bioavailability 100%); also available intravenously
   ii. Half-life is about 30 hours; primarily eliminated unchanged in the urine
c. Adverse effects
   i. Nausea, abdominal pain, headache, reversible alopecia
   ii. Elevated liver function tests
d. Drug interactions (CYP3A4 inhibitor at more than 400 mg/day and CYP2C9 inhibitor at lower doses)
   i. Cyclosporine
   ii. Phenytoin
   iii. Warfarin
e. Dosing
   i. Oral candidiasis: 100–200 mg/day
   ii. Esophageal candidiasis: 200–400 mg/day
   iii. Invasive candidiasis: 400–800 mg/day
   iv. Acute cryptococcal meningitis: 400–800 mg/day
   v. Cryptococcal meningitis prophylaxis: 200 mg/day

3. Itraconazole (Sporanox)
   a. Spectrum of activity
      i. *Candida* spp. (usually just *C. albicans*), *Cryptococcus, Aspergillus, Blastomyces, Histoplasma,* dermatophytes
      ii. Clinical use
         (a) Onychomycosis
         (b) Histoplasmosis
         (c) Aspergillosis
         (d) Blastomycosis
   b. Pharmacokinetics
      i. Capsule absorption improves with food; solution should be taken on an empty stomach.
      ii. Half-life is about 20 hours; extensively metabolized; hydroxy itraconazole is active.
   c. Adverse effects
      i. Nausea, abdominal pain, headache, rash
      ii. Elevated liver function tests, potential fulminant hepatitis
      iii. Caution in heart failure (avoid doses of 400 mg/day or greater; do not use for treatment of onychomycosis if heart failure)

d. Drug interactions (CYP2C9, CYP2C19 and CYP3A4 inhibitor)
   i. Antacids, H_2-blockers, proton pump inhibitors, didanosine (GI absorption)
   ii. Cyclosporine
   iii. Digoxin (decreases digoxin volume of distribution)
   iv. Phenytoin
   v. Warfarin
   vi. PIs
   vii. HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors
e. Dosing: 200 mg three times daily for 3 days and then 100–200 mg/day. Oral capsules with food; oral solution without food
f. Therapeutic Drug Monitoring (TDM)
   i. TDM appropriate for most patients receiving itraconazole
   ii. Trough concentrations taken 7-14 days after starting therapy or making dose adjustments.
   iii. Target concentrations > 0.5 mg/L for prophylaxis and > 1 mg/L for treatment.

4. Voriconazole (Vfend)
   a. Spectrum of activity
      i. *Candida* spp., *Aspergillus, Fusarium, Scedosporium, Histoplasma, Cryptococcus*
      ii. Clinical use
         (a) Resistant *Candida* infections (especially *C. glabrata* and *C. krusei*)
         (b) Aspergillosis
         (c) Histoplasmosis
   b. Pharmacokinetics
      i. Oral absorption about 95%; also available intravenously
      ii. Half-life is about 6 hours; extensively metabolized; CYP2C9, CYP3A4, CYP2C19
   c. Adverse effects
      i. Abnormal vision 30% (abnormal vision, color changes, photophobia). Short-term (20–30 minutes) effects on retina. Dose related. Not studied for more than 28 days of therapy
      ii. Elevated liver function tests, rash, nausea, corrected QT interval (QTc) prolongation, alkaline phosphatase elevations, skin cancers
   d. Drug interactions (CYP3A4 and CYP2C9 inhibitor and substrate; see Table 13)
   e. Dosing
      i. Aspergillosis: Loading dose, 6 mg/kg two times intravenously (infuse for 2 hours); maintenance dose, 4 mg/kg every 12 hours intravenously (infuse for 2 hours)
      ii. Candidiasis and candidemia: 400 mg orally or intravenously every 12 hours for two doses, then 200 mg every 12 hours
         (a) For patients who are receiving phenytoin, increase dose to 5 mg/kg every 12 hours intravenously or 200–400 mg every 12 hours orally.
         (b) Dose reduction for moderate or severe cirrhosis: After loading dose, decrease dose by 50% in Child-Pugh class A/B. No information for patients in Child-Pugh class C
         (c) No adjustment of the oral dose for renal insufficiency; patients with CrCl less than 50 mL/minute/1.73 m^2 should not receive the intravenous product because of accumulation of the intravenous vehicle sulfobutyl ether-β-cyclodextrin
         (d) Therapeutic drug monitoring indicated because of polymorphism in CYP2C19 metabolism
   f. Therapeutic Drug Monitoring (TDM)
      i. TDM appropriate for most patients receiving voriconazole (esp. pediatrics, patients with toxicity, and patients receiving interacting drugs).
      ii. Consider monitoring when transitioning from IV to oral (esp. in obesity)
      iii. Trough concentrations taken 4-5 days after starting therapy or making dose adjustments.
      iv. Target concentrations > 0.5 mg/L for prophylaxis and > 1-2 mg/L for treatment.

Table 13. Drug Interactions Reported with Voriconazole

Drug	Effect	Recommendation
Rifampin (CYP inducer)	↓ Voriconazole	Coadministration contraindicated
Rifabutin (CYP inducer)	↓ Voriconazole ↑ Rifabutin	Coadministration contraindicated
Carbamazepine (CYP inducer)	↓ Voriconazole	Coadministration contraindicated
Barbiturates, long acting (CYP inducers)	↓ Voriconazole	Coadministration contraindicated
Ergot alkaloids	↑ Ergot alkaloids ↑ Risk ergotism	Coadministration contraindicated
Sirolimus (CYP3A4 substrate)	↑ Sirolimus	Coadministration contraindicated
Cyclosporine (CYP3A4 substrate)	↑ Cyclosporine	Reduce cyclosporine dose by half when initiating voriconazole Monitor levels closely Increase cyclosporine dose as necessary when voriconazole is discontinued
Tacrolimus (CYP3A4 substrate)	↑ Tacrolimus	Reduce tacrolimus dose to one-third of initial dose when initiating voriconazole Monitor levels closely Increase tacrolimus dose as necessary when voriconazole is discontinued
Omeprazole (CYP2C19 inhibitor, CYP2C19 and CYP3A4 substrate)	↑ Voriconazole ↑ Omeprazole	In patients receiving omeprazole doses ≥ 40 mg, reduce omeprazole dose by half
Warfarin (CYP2C9 substrate)	↑ Warfarin ↑ PT	Closely monitor PT/INR and adjust warfarin dose as needed

INR = international normalized ratio; PT = prothrombin time.

5. Posaconazole (Noxafil)
    a. Spectrum of activity
        i. *Candida* spp., *Cryptococcus*, *Trichosporon*, *Aspergillus*, *Fusarium*, *Zygomycetes*
        ii. Clinical use
            (a) *Candida* infections
            (b) Aspergillosis
            (c) Zygomycoses
            (d) Fusariosis
    b. Pharmacokinetics
        i. Oral absorption of suspension increased by a high-fat meal
        ii. Oral tablet formulation: Food has less impact on absorption.
        iii. Half-life is about 24–30 hours; primarily eliminated unchanged in the feces
    c. Adverse effects
        i. Nausea, vomiting, diarrhea
        ii. Elevated liver function tests, rash, hypokalemia, thrombocytopenia
        iii. QTc prolongation
    d. Drug interactions: CYP3A4 inhibitor; decreased posaconazole suspension absorption with proton pump inhibitors and H_2-blockers

e. Dosing: Oropharyngeal candidiasis, 100 mg/day suspension; refractory oropharyngeal candidiasis, 400 mg twice daily suspension; prophylaxis of invasive fungal infections in neutropenic and patients with graft-versus-host disease, 200 mg three times daily (suspension), 300 mg daily (tablet or intravenous)

6. Isavuconazonium (Cresemba)
   a. Spectrum of activity
      i. *Candida* spp., *Cryptococcus, Aspergillus, Mucorales, Fusarium, Histoplasma, Blastomyces*
      ii. Clinical use
         (a) Aspergillosis
         (b) Mucormycosis
   b. Pharmacokinetics
      i. Prodrug that is rapidly hydrolyzed in the blood to isavuconazole
      ii. Oral absorption is complete (take with or without food) and protein binding is greater than 99%.
      iii. Half-life is about 130 hours; metabolized primarily by CYP3A4
   c. Adverse effects
      i. Nausea, vomiting, diarrhea
      ii. Elevated liver function tests, hypokalemia, cough, peripheral edema, back pain
   d. Drug interactions: CYP3A4 substrate and moderate inhibitor; P-glycoprotein mild inhibitor; increased isavuconazole with PIs; decreased isavuconazole with rifampin
   e. Dosing: 372 mg (200 mg isavuconazole) every 8 hours for six doses (loading dose) followed by 372 mg (200 mg isavuconazole) daily (maintenance dose)

C. Echinocandins
   1. Mechanism of action: Inhibits synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall
   2. Caspofungin (Cancidas), micafungin (Mycamine), anidulafungin (Eraxis)
      a. Spectrum of activity
         i. *Candida* spp. (weak against *C. parapsilosis*), *Aspergillus*
         ii. Clinical use
            (a) *Candida:* Invasive candidiasis, candidemia, intra-abdominal abscesses, peritonitis, and pleural space infections
            (b) Esophageal candidiasis
            (c) Invasive aspergillosis (refractory to or intolerant of other therapies)
      b. Pharmacokinetics
         i. Only available intravenously
         ii. Half-life of about 1–2 days; caspofungin and micafungin hepatically metabolized; anidulafungin chemically degraded in the blood
         iii. Low urine concentrations
      c. Adverse effects: Infusion site–related reactions, headache, GI symptoms
      d. Drug interactions
         i. Caspofungin: Avoid concomitant use with cyclosporine or tacrolimus.
         ii. Micafungin: Avoid concomitant sirolimus or nifedipine.
         iii. Anidulafungin: None
      e. Dosing
         i. Caspofungin: 70 mg once intravenously, followed by 50 mg/day intravenously (lower dose for Child-Pugh class B: 70 mg loading, then 35–50 mg daily)
         ii. Micafungin: Candidemia 100 mg/day; esophageal candidiasis or aspergillosis 150 mg/day
         iii. Anidulafungin: 200 mg once intravenously, followed by 100 mg/day intravenously

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: D

The patient should be treated at this time; a potent combination ART should be initiated in all HIV-infected patients, regardless of CD4 count (Answer A is incorrect). Combination therapy of tenofovir, emtricitabine, and raltegravir is a recommended initial therapeutic regimen (Answer D is correct). Regimens without an NNRTI, PI, or INSTI are not indicated for HIV (Answer B is incorrect). The regimen of abacavir, lamivudine, and atazanavir/ritonavir is not a recommended or alternative option. It should only be used if recommended or alternative options are not appropriate and should definitely not be first-line therapy (Answer C is incorrect).

2. Answer: B

A patient taking abacavir should be screened for the presence of the *HLA-B*5701* allele before initiating therapy. If the patient is positive for this allele, the risk of hypersensitivity reactions is increased (Answer B is correct). Although abacavir may increase AST and ALT concentrations, the incidence of hepatotoxicity is extremely low and these labs do not need to be checked before starting therapy. (Answer A is incorrect). Endocrine disturbances (e.g., hyperglycemia, fat redistribution, lipid abnormalities) are more associated with PIs (Answer C is incorrect). Abacavir does not cause hyperbilirubinemia; therefore, the patient need not be monitored for this (although a patient taking atazanavir does) (Answer D is incorrect).

3. Answer: A

When the CD4 count decreases to 135 cells/mm^3, the patient should receive primary prophylactic treatment against PCP (CD4 count less than 200 cells/mm^3) (Answer A is correct). Primary prophylaxis is necessary for MAC when the CD4 count is less than 50 cells/mm^3 (Answer D is incorrect). For CMV, patients with CD4 counts less than 50 cells/mm^3 should receive regular funduscopic examinations (Answer C is incorrect). In general, primary prophylaxis is not used for cryptococcal meningitis (Answer B is incorrect).

4. Answer: C

Although pentamidine would be an appropriate therapeutic option for a patient who is HIV positive with PCP, the optimal empiric therapy is trimethoprim/sulfamethoxazole intravenously with adjuvant prednisone therapy for 21 days (Answer A is incorrect and answer C is correct). The regimen may be changed to trimethoprim/sulfamethoxazole orally after the patient has clinical improvement. Although trimethoprim/sulfamethoxazole is the drug of choice for PCP, adjuvant prednisone therapy is indicated because the patient's A-a gradient is 55, and his PO_2 is less than 70 mm Hg (Answer B is incorrect). Atovaquone is indicated only for patients with mild to moderate PCP who cannot tolerate trimethoprim/sulfamethoxazole. This patient does not meet this criterion (Answer D is incorrect).

5. Answer: B

Patients with cryptococcal meningitis should ideally be treated with liposomal amphotericin and flucytosine for at least 2 weeks, followed by fluconazole for at least 8 weeks (Answer B is correct). Although amphotericin B deoxycholate with fluconazole is an alternative, this is not the best option (Answer A is incorrect). Fluconazole alone is also an alternative but should only be used when none of the amphotericin products is an option for therapy (Answer C is incorrect). Because of the higher mortality when ART is begun early in cryptococcal meningitis therapy, initiation of ART should be delayed until 5 weeks after beginning appropriate antifungal therapy (Answer D is incorrect).

6. Answer: B

Maintenance therapy for cryptococcal meningitis with fluconazole can be discontinued after a minimum of 1 year of long-term maintenance therapy if the CD4 count increases to more than 100 cells/mm^3 for 3 months or longer after potent combination ART (Answer B is correct and answer D is incorrect). Because this patient's CD4 counts have been greater than 100 cells/mm^3 for at least 3 months, maintenance therapy can be discontinued after he has been treated for 1 year (Answers A and C are incorrect).

7. Answer: B

For the treatment of MAC, azithromycin plus ethambutol for at least 12 months is the best therapeutic combination; this combination includes one of the newer macrolides and a second agent (ethambutol is usually the preferred second agent) (Answer B is correct). Therapy may be discontinued after 12 months if CD4 counts increase with potent combination ART and if the patient

is asymptomatic. Clarithromycin plus ethambutol for 2 weeks, followed by maintenance with clarithromycin alone, is incorrect because there is no induction therapy followed by maintenance monotherapy for MAC (Answer A is incorrect). A therapeutic regimen of clarithromycin plus isoniazid is not the best because isoniazid has no activity against MAC (Answer C is incorrect). Although ethambutol plus rifabutin has activity against MAC, the current recommendations are that all therapeutic regimens include either azithromycin or clarithromycin; therefore, the ethambutol plus rifabutin regimen is not the treatment of choice (Answer D is incorrect).

8. Answer: D

A patient with an induration greater than 15 mm after a TST for TB needs to be assessed for treatment. Because this patient works at a high-risk congregate setting (i.e., the long-term care facility), he needs to be treated (Answer A is incorrect). The booster effect is a phenomenon associated with an initial small reaction causing immunologic stimulation, followed by a larger reaction with a subsequent test (Answer B is incorrect). This patient had an initial large reaction (18-mm induration). Age is not a factor to consider in treating latent TB (Answer C is incorrect). Initiating isoniazid 300 mg/day orally for 9 months is the best recommendation for managing this patient's positive TST (Answer D is correct).

9. Answer: C

This patient's HIV medications should be changed (rifampin will induce the metabolism of darunavir and ritonavir) (Answer A is incorrect). He should not receive a PI or an NNRTI (except for efavirenz) with rifampin. Patients who are HIV positive should be initiated on four drugs for TB, and darunavir should not be used with rifampin (Answer B is incorrect). The best recommendation is isoniazid, rifabutin, pyrazinamide, and ethambutol, with a lower dose of rifabutin; it includes the four drugs for TB and a lower dose of rifabutin (because of darunavir/ritonavir inhibition) (Answer C is correct). The darunavir/ritonavir dose does not need to be changed when rifabutin is added (Answer D is incorrect).

10. Answer: C

For this patient, only the rifamycin and isoniazid need to be continued after 2 months of therapy with the four drugs for TB (Answer A is incorrect). The regimen can be simplified to a rifamycin and isoniazid after 2 months, but the recommended treatment duration is 6 months (Answers B and D are incorrect). The concentrations of HIV RNA should be monitored closely because of potential alterations in drug concentrations of the PI (Answer C is correct).

11. Answer: B

Candida krusei is an organism that is frequently resistant to azole antifungals, including fluconazole and voriconazole; therefore, those agents should not be used in this situation (answers A and D are incorrect). The best choice would be either an echincocandin or amphotericin product (although the newer azoles, posaconazole, and isavuconazole do have some activity against *C. krusei*). Given its lower side effect profile and lack of adjustments needed for renal or hepatic dysfunction, micafungin is the best choice in this situation (answer B is correct). The length of therapy is also correct, treatment for 14 days after the first negative blood culture. Although an amphotericin B lipid formulation would be a second-line option, the higher incidence of side effects associated with its use make it not the best choice (answer C is incorrect).

12. Answer: D

Onychomycosis needs to be treated for a long period of time, generally 3 months. Although fluconazole is active against the organisms that cause onychomycosis and systemic therapy is generally best, a 14-day course would not be long enough to effectively treat the infection (answer A is incorrect). Itraconazole is one of the drugs of choice for onychomycosis, in either a continuous or pulse therapeutic regimen. However, once again, 28 days is not long enough for treatment (answer B is incorrect). There are a number of different topical antifungal medications that can be used for onychomycosis. However, miconazole cream is not one of them. Also, topical treatment requires longer therapy than systemic treatment (answer C is incorrect). Terbinafine is one of the drugs of choice for onychomycosis and the treatment duration, 3 months, is correct (answer D is correct).

13. Answer: B

Micafungin has activity against *Aspergillus* and is the best option for this patient because it does not require dosage adjustment for renal dysfunction and has limited drug interactions (Answer B is correct). Lipid

amphotericin has activity against *Aspergillus* and could be used for this infection, but because of its renal toxicity, lipid amphotericin is not the best choice in this patient with acute renal failure (Answer A is incorrect). Fluconazole has no activity against *Aspergillus* and could potentially interact with the some of the drugs the patient is receiving (Answer C is incorrect). Voriconazole has activity against *Aspergillus*, but it significantly interacts with several of the drugs the patient is receiving (atorvastatin, dronedarone, warfarin, carbamazepine), making it a less than ideal choice in this patient (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

Transmission of HIV to a child is decreased if the mother's viral load is decreased. The benefits of therapy far outweigh the risk (Answer A is incorrect). A potent combination ART regimen given throughout the pregnancy is the most appropriate therapeutic regimen for an asymptomatic patient with HIV who is pregnant (even in the first trimester) and has a low CD4 count and high viral load (Answer D is correct). Although zidovudine 300 mg twice daily orally throughout the pregnancy, followed by zidovudine during labor and to the child for 6 weeks, was the regimen originally studied to decrease HIV transmission, potent combination ART is indicated because of the patient's low CD4 count and high viral load; therefore, single-drug therapy is inappropriate (Answer B is incorrect). A single dose of nevirapine at the onset of labor will not affect viral load or lower the risk of HIV transmission as much as potent combination ART throughout the pregnancy (Answer C is incorrect).

2. Answer: A

The patient should be told that dolutegravir can cause insomnia (Answer A is correct). This patient should be told to talk to a pharmacist about the current combination therapy because there are many drug interactions with antiretroviral agents. Neither dolutegravir nor tenofovir inhibit CYP3A4 (Answer C is incorrect). In addition, informing the patient to cut the dose in half if there are adverse effects is incorrect because antiretroviral drugs, should never be used below the recommended dose (Answer B is incorrect). Informing the patient that tenofovir and emtricitabine cause additive peripheral neuropathy is incorrect because neither of these drugs is associated with that adverse effect (Answer D is incorrect).

3. Answer: B

Patients with cryptococcal meningitis should always receive maintenance therapy (Answer A is incorrect). One of the principles of treating AIDS-related illnesses is that the infections are seldom curable, and generally long-term secondary prevention is required. Weekly amphotericin B has been studied for secondary prophylaxis, but fluconazole is the better agent because of its ease of administration and lower toxicity (Answer B is correct and answer C is incorrect). The agents that are effective for PCP prophylaxis have no activity against *Cryptococcus (*Answer D is incorrect).

4. Answer: C

The number of patients needed to treat with isoniazid over rifampin to prevent one progression to active disease is $200 = 1/(0.008 - 0.003)$ (Answers A and B are incorrect and answer C is correct). The only information needed is the absolute risk in both groups, which is provided (Answer D is incorrect).

5. Answer: D

Pyrimethamine plus clindamycin and leucovorin for 6 weeks is the correct choice for treating toxoplasmosis in a patient who is HIV positive, not taking antiretrovirals, and taking dapsone for PCP prophylaxis (Answer D is correct). Atovaquone is not first-line therapy, although data support its effectiveness in combination with sulfadiazine or pyrimethamine (Answer A is incorrect); trimethoprim/sulfamethoxazole is not effective for treatment or secondary prophylaxis of toxoplasmosis (Answer B is incorrect). Pyrimethamine and sulfadiazine are the first-line agents for toxoplasmosis; however, leucovorin should always be used with pyrimethamine to prevent myelosuppression (Answer C is incorrect).

6. Answer: D

Fluconazole has no activity against aspergillus, so it would not be an option for therapy (Answer A is incorrect). Although voriconazole has activity against aspergillus, there is a significant interaction with rifampin, resulting in lower voriconazole concentrations (Answer B is incorrect). Isavuconazonium does have activity against aspergillus, but levels are significantly decreased in a patient receiving rifampin (Answer C is incorrect). Amphotericin lipid formulation would be the best option because of its activity against aspergillus and lack of drug interaction with any of the TB medications (Answer D is correct).

7. Answer: B

Because the patient is symptomatic and her sputum is acid-fast bacillus positive, she should be treated for an active TB infection. The recommended therapy for active TB is isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 more months (Answer B is correct).

Patients should be initiated on at least three antibiotics for the first 2 months (Answers A and C are incorrect). Although fluoroquinolones have some activity against TB, their use as first-line monotherapy is inappropriate (Answer D is incorrect).

8. Answer: C
Data are continuous and probably normally distributed (given the large population of 350 patients in the study); therefore, a parametric test is indicated. The t-test is the best parametric test for comparing two groups (Answer C is correct). Although an analysis of variance is a parametric test, it is used to compare more than two groups (Answer A is incorrect). A chi-square test is used to compare nominal or categorical data between two groups (Answer B is incorrect). The end points in this study are continuous and should therefore not be compared using this statistical test. The Wilcoxon rank sum test is a nonparametric analog to the t-test (Answer D is incorrect).

9. Answer: A
Valganciclovir therapy should be continued in an HIV-positive patient with CMV retinitis until the patient's CD4 count is above 100 cells/mm^3 for at least 3 months (Answer A is correct, answers B, C and D are incorrect). There is no minimum duration of therapy for CMV retinitis, as there is with MAC or cryptococcal infections. Therapy would need to be reinitiated if his CD4 count fell back below 100 cells/mm^3. In patients with CMV retinitis, all lesions must be inactive and the decision to stop maintenance treatment made in collaboration with an ophthalmologist.

10. Answer: B
All azole antifungals interact with CYP enzymes. However, fluconazole has less CYP3A4 inhibition than the other azole antifungals (Answer B is correct). It interacts with CYP2C9 at lower doses, but it interacts with CYP3A4 only at doses of 400 mg/day or higher. All other azole antifungals interact with CYP3A4 at typical therapeutic doses (Answer A, C and D are incorrect).

11. Answer: C
Because the patient has a sulfa allergy, trimethoprim/sulfamethoxazole is not an option, even though the dose is correct (Answer A is incorrect). All of the other agents are potential options. However, the dapsone dose is incorrect. When used alone it must be dosed daily (Answer B is incorrect). Moreover, pentamidine is difficult to administer because it must be done by nebulization (Answer D is incorrect). Therefore, the best choice is atovaquone (Answer C is correct).

12. Answer: A
Given the fact that this patient is hospitalized and his infection is worsening, this can be considered a moderate to severe case of Histoplasmosis. The correct regimen is 1-2 weeks of an amphotericin B lipid formulation followed by itraconazole to complete a 12-week course (Answer A is correct). The echinocandins appear to be ineffective against Histoplasma so micafungin should not be used (answer B is incorrect). Although both voriconazole and isavuconazole have activity against Histoplasma they currently aren't recommended based on limited to no clinical data to back up their use. Voriconazole also has a lot of drug interactions (as does itraconazole) and isavuconazole is much more expensive (answers C and D are incorrect).

13. Answer: B
This patient has active tuberculosis as demonstrated by his symptoms, positive sputum, and positive IGRA test. Patients with active tuberculosis should be treated with 4 drugs (rifampin, isoniazid, pyrazinamide, ethambutol) for 2 months and 2 drugs (rifampin and isoniazid) for 4 months (answers C and D are incorrect). Although a regimen administered 2 and 3 times weekly is optional, it is not the recommended therapy (answer A is incorrect). Ideally, active tuberculosis treatment should be given either daily or 5 times weekly (Answer B is correct).

Neurology

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Neurology

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Learning Objectives

1. Identify seizure types and status epilepticus.
2. Determine appropriate use of antiepileptic drugs on the basis of their activity, adverse effects, and drug interactions for epilepsy and status epilepticus.
3. Establish appropriate interventions for primary and secondary prevention of stroke.
4. Determine appropriate treatment for acute stroke.
5. Initiate and monitor pharmacotherapy for Parkinson disease.
6. Differentiate between regimens for acute and prophylactic treatment of migraine, tension, and cluster headaches.
7. Identify appropriate therapies for individuals with multiple sclerosis.
8. Establish appropriate treatment for peripheral neuropathy.

Abbreviations in This Chapter

ASM	Antiseizure medication
CNS	Central nervous system
GABA	γ-Aminobutyric acid
JME	Juvenile myoclonic epilepsy
MAO-B	Monoamine oxidase type B
MS	Multiple sclerosis
NSAID	Nonsteroidal anti-inflammatory drug
TIA	Transient ischemic attack

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. E.S. is a 25-year-old electrician. He has had several episodes of memory lapses. His wife reports lip smacking and chewing movements during these spells. An electroencephalogram (EEG) reveals focal epileptiform spike waves. Which medication would be best for E.S.?
   A. Ethosuximide.
   B. Levetiracetam.
   C. Phenobarbital.
   D. Clobazam.

2. B.V. is a 48-year-old woman brought to your emergency department for the treatment of status epilepticus. Her blood glucose is 50 mg/dL on fingerstick. Which medication is the best next treatment step for B.V.?
   A. Lorazepam.
   B. Dextrose.
   C. Thiamine.
   D. Diazepam.

3. J.H. is a 42-year-old man with focal onset seizures with loss of awareness for which he was prescribed levetiracetam. He comes to the pharmacy where you work with concerns of agitation. He says his wife is also concerned because he is very irritable and, at times, depressed. Which best assesses J.H.'s condition?
   A. Discontinue levetiracetam; he is having adverse effects.
   B. Increase the levetiracetam dose; he is having focal seizures.
   C. Continue levetiracetam; it is controlling his seizures.
   D. Obtain a levetiracetam serum concentration; he is probably supratherapeutic.

Questions 4 and 5 pertain to the following case.

T.O. is a 68-year-old man who suddenly lost consciousness at home. His partner calls 911, and emergency medical technicians arrive within 10 minutes. According to the medical record, he experienced slurred speech and right arm weakness about 30 minutes before losing consciousness. He is treated for hypertension.

4. Which test would be best before initiating pharmacotherapy for T.O.?
   A. Cerebral angiogram.
   B. Computed tomography (CT) scan of head.
   C. Coagulation panel.
   D. Echocardiogram.

5. T.O. was given a diagnosis of a major ischemic stroke and treated with alteplase. He regains consciousness and is transferred to rehabilitation. Which treatment would be best for 3 months to prevent another stroke?
   A. Aspirin and clopidogrel.
   B. Aspirin and dipyridamole.

C. Apixaban.
D. Warfarin.

Questions 6 and 7 pertain to the following case.
P.P. is a 75-year-old woman who was given a diagnosis of Parkinson disease 8 years ago. During this visit to the clinic, she notes that her movements are slower and she feels stiffer. She has also experienced a worsening gait with two or three falls in the past 6 months. Her writing has also become small and illegible. She takes carbidopa/levodopa 25/100 mg 2 tablets four times daily.

6. Which of P.P.'s symptoms would be controlled by pharmacotherapy?
   A. Gait disturbances.
   B. Falls.
   C. Hand writing.
   D. Rigidity.

7. P.P. notes that her symptoms seem worse before her next dose of carbidopa/levodopa. Which agent would best be added at this visit?
   A. Rasagiline.
   B. Entacapone.
   C. Apomorphine.
   D. Quetiapine.

8. W.S. is a 70-year-old man with newly diagnosed Parkinson disease who is initiated on carbidopa/levodopa. His symptoms are well controlled, but he has concerns of nausea and vomiting. Which is the best intervention to reduce his nausea and vomiting?
   A. Initiate promethazine
   B. Initiate metoclopramide.
   C. Decrease carbidopa/levodopa.
   D. Initiate trimethobenzamide.

Questions 9 and 10 pertain to the following case.
R.M. is a 42-year-old man with headaches, which he describes as a tight band around his head. The headaches occur three or four times a week.

9. Which drug is best for R.M. to use for his headaches?
   A. Naproxen.
   B. Sumatriptan.
   C. Dihydroergotamine.
   D. Lithium.

10. If R.M. needs a drug for tension headache prophylaxis, which agent is best to recommend?
   A. Amitriptyline.
   B. Valproate.
   C. Topiramate.
   D. Frovatriptan.

Questions 11–13 pertain to the following case.
L.M. is a 43-year-old man who received a diagnosis of relapsing-remitting multiple sclerosis (MS) 2 years ago. He has taken glatiramer acetate since then. However, his exacerbations have not discernibly decreased. He has spasticity in his legs, which has caused several falls in the past month, and fatigue that worsens as the day progresses.

11. Which drug is best for L.M.'s MS?
   A. Cyclophosphamide.
   B. Methylprednisolone.
   C. Azathioprine.
   D. Fingolimod.

12. Which drug is best for L.M.'s spasticity?
   A. Diazepam.
   B. Baclofen.
   C. Carisoprodol.
   D. Metaxalone.

13. Which drug is best for L.M.'s fatigue?
   A. Propranolol.
   B. Lamotrigine.
   C. Amantadine.
   D. Ropinirole.

Questions 14 and 15 pertain to the following case.
B.T. is a 62-year-old man with obesity (weight 122 kg [270 kg]) who comes to the clinic with concerns of burning in the soles of his feet. These symptoms began about 3 months ago. They are worse at night and keep him from sleeping. On examination, he has decreased sensation in both feet up to the ankles bilaterally and good strength throughout his feet and legs. Ankle

reflexes are decreased. He has hypertension treated with lisinopril 10 mg/day.

14. Which most likely caused B.T.'s pain and decreased sensation?
    A. Diabetic neuropathy.
    B. Chronic inflammatory demyelinating polyneuropathy.
    C. Entrapped nerve.
    D. Genetic neuropathy.

15. Which treatment is best for B.T.'s symptoms?
    A. Carbamazepine 600 mg at bedtime.
    B. Lidocaine 5% patch applied to soles of feet at bedtime and removed in the morning.
    C. Acetaminophen 325 mg every 4 hours as needed.
    D. Valproate 250 mg twice daily.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-Specific Pharmacotherapy
    a. Tasks 1:1–5, 1:7–8, 1:11–12, 3:2, 4:1–2, 4:5–7

I. EPILEPSY

A. Epidemiology
   1. Epilepsy is the fourth most common neurologic disorder. Ten percent of the U.S. population will have a seizure. Around 7.6 of 1000 individuals will develop epilepsy at some point in their lives (World Health Organization. *Epilepsy: A Public Health Imperative*, 2019).
   2. About 50 million people worldwide have epilepsy.
   3. About 50% of patients with a new diagnosis become seizure free on their first treatment, with up to 70% becoming seizure free after treatment adjustment and 30% continuing to have seizures (Neurology 2012;78:1548-54).

B. Classification of Seizures: Seizures are traditionally classified according to the International League Against Epilepsy scheme, adopted in 1981, with modifications in 2001 and 2010. The 2017 classification scheme for seizures was changed and adopted by the International League Against Epilepsy
   1. Focal onset seizures start in an area or network of cells on one side of the brain.
      a. Focal seizures can further be classified as with or without loss of awareness, motor or nonmotor, and focal to bilateral tonic-clonic.
      b. The terms *simple partial seizure*, *complex partial seizure*, and *secondarily generalized seizure* have been eliminated from official classification; however, they are still used commonly to describe seizures.
   2. Generalized onset seizures engage or involve networks on both sides of the brain at the onset.
      a. Nonmotor (absence): Typical nonmotor seizures are brief and abrupt, last 10–30 seconds, and occur in clusters. They usually result in a short loss of consciousness, or patients may stare, be motionless, or have a distant expression on their face. Electroencephalograms (EEGs) during seizure activity usually show 3-Hz spike-and-wave complexes. Nonmotor seizures can be further classified as typical, atypical, myoclonic absence, and eyelid myoclonia.
      b. Motor-myoclonic: Consist of brief, rapid jerking movements of the entire body or the upper and occasionally lower extremities. Motor-myoclonic seizures can be further classified as myoclonic, myoclonic atonic, or myoclonic tonic.
      c. Motor-tonic clonic: Typically, a motor tonic-clonic seizure has five phases: flexion, extension, tremor, clonic, and postictal. During the flexion phase, the patient's mouth may be held partly open, and the patient may have upward eye movement, involvement of the extremities, and loss of consciousness. In the extension phase, the patient may be noted to extend his or her back and neck; have contraction of thoracic and abdominal muscles; be apneic; and have flexion, extension, and adduction of the extremities. The patient may cry out as air is forced from the lungs in this phase. The tremor phase occurs as the patient goes from tonic rigidity to tremors and then to a clonic state. During the clonic phase, the patient will have rhythmic jerks. The entire seizure usually lasts 1–3 minutes. After the seizure, the patient may be postictal. During this time, the patient can be difficult to arouse or very somnolent. Before the seizure, a patient may have a prodrome but not an aura.
      d. Motor-clonic: Only the clonic phase of a motor tonic-clonic seizure; rhythmic, repetitive, jerking muscle movements
      e. Motor-tonic: Only the flexion or extension phases of a motor tonic-clonic seizure
      f. Motor-atonic: Characterized by a loss of muscle tone. Motor-atonic seizures are often described as drop attacks, in which a patient loses tone and falls to the ground.
   3. Seizures of unknown onset: Onset of the seizure cannot be determined as focal or generalized
      a. Motor
      b. Nonmotor
      c. Unclassified

4. Epilepsy is a disease of the brain defined by any of the following conditions:
   a. Two unprovoked (or reflex) seizures occurring more than 24 hours apart;
   b. One unprovoked (or reflex) seizure and a probability of subsequent seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;
   c. Diagnosis of an epilepsy syndrome (Epilepsia 2014;55:475-82)
5. Status epilepticus is caused either by the failure of the mechanisms responsible for seizure termination or by the initiation of mechanisms, which lead to abnormally prolonged seizures after 5 minutes. At this point, treatment for status epilepticus should be initiated. After 30 minutes, status epilepticus can have long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks (depending on the type and duration of seizures). Mortality is up to 20% for status epilepticus (Epilepsia 2015;56:1515-23).
6. Nonepileptic seizures are paroxysmal nonepileptic episodes (based on EEG) resembling epileptic seizures that can be organic or psychogenic.
7. Other associated symptoms
   a. Prodrome: Awareness of an impending seizure before it occurs. The prodrome may consist of headache, insomnia, irritability, or a feeling of impending doom.
   b. Aura: A focal seizure, without loss of consciousness, consisting of sensory or autonomic symptoms that may precede evolution to a bilateral, convulsive seizure. Patients may have feelings of fear, embarrassment, or déjà vu. Automatic behavior (automatism) and psychic symptoms may occur. Automatisms may include lip smacking, chewing, swallowing, abnormal tongue movements, scratching, thrashing of the arms or legs, fumbling with clothing, and snapping the fingers. Psychic symptoms include illusions, hallucinations, emotional changes, dysphasia, and cognitive problems.

C. Diagnosis
   1. Physical examination should occur, with special attention given to neurologic findings. The neurologic examination may include examination of the head, vision, cranial nerves, motor function, cerebellar function, and sensory function.
   2. Laboratory tests are based on the history and physical examination results; a full diagnostic panel is unnecessary in many patients. Because metabolic causes of seizures are common, serum glucose, electrolytes, calcium, complete blood cell counts (CBCs), and renal function tests may be necessary. A toxicology screen may also be prudent.
   3. EEGs are used to help confirm the diagnosis, classify seizures, locate the site of the seizures, and select the best seizure medication. The best time for an EEG is while the patient is having seizures. If doing an EEG is not possible during seizures, the EEG should be done as soon after the seizure as possible. Depending on the clinical situation, an EEG may be obtained under normal conditions, when the patient is sleep deprived, or when the patient is asleep. Patients whose seizures are difficult to diagnose or control may need prolonged video–EEG monitoring or ambulatory EEG. Keep in mind that although an interictal (when the patient is not having clinical seizures) EEG may be normal, this does not preclude the diagnosis of epilepsy.
   4. Magnetic resonance imaging is the neuroimaging technique of choice for epilepsy. CT scanning can help find brain lesions when magnetic resonance imaging cannot be done in a timely fashion.

D. Treatment
   1. Medications (see Tables 1–5)
      a. Benzodiazepines
         i. Mechanism of action: Augment γ-aminobutyric acid (GABA)-mediated chloride influx
         ii. Tolerance may develop: Usually used as adjunctive, short-term therapy
         iii. Most commonly used drugs: Chlorazepate (Tranxene), clobazam (Onfi), clobazam oral film (Sympazan), clonazepam (Klonopin), diazepam (Valium), and lorazepam (Ativan)

iv. All benzodiazepines are controlled substances, scheduled as C-IV.
v. For acute repetitive seizures: Intranasal midazolam (Nayzilam), intranasal diazepam (Valtoco)
vi. Nonepileptic indications: Chlorazepate (anxiety disorders, anxiety), clonazepam (panic disorder with or without agoraphobia), lorazepam (anxiety disorders, anxiety, alcohol withdrawal)

b. Brivaracetam (Briviact)
i. Mechanism of action: Unknown mechanism, but has high affinity for synaptic vesicle protein 2A
ii. Adverse effects: Somnolence, sedation, dizziness, fatigue
iii. Drug interactions: Carbamazepine, phenobarbital, phenytoin

c. Cannabidiol (Epidiolex)
i. The only U.S. Food and Drug Administration (FDA)-approved cannabis product for epilepsy
ii. Approved for seizures caused by Dravet syndrome, tuberous sclerosis, and Lennox-Gastaut syndrome
iii. Adverse effects: Sedation, drowsiness, diarrhea, intestinal cramping, increased liver transaminase (11% of patients); 3% of patients discontinued because of increased liver function tests
iv. Metabolized by cytochrome P450 (CYP) 2C19 and 3A4
v. Inhibitor of UGT1A9, UGT2B7, CYP2C8, CYP2C9, CYP2C19
vi. Possible inhibitor of CYP1A2, CYP2B6
vii. Inhibits metabolism of desmethylclobazam, the active metabolite of clobazam
viii. Increased hepatotoxicity with concomitant valproate
ix. Maintenance dose 10–20 mg/kg/day in two divided doses, initiate with 5 mg/kg/day and titrate to optimal dose
x. Schedule V drug

d. Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Teril)
i. Mechanism of action: Fast sodium channel blocker
ii. Pharmacokinetics: Enzyme inducer, autoinduction
iii. Adverse effects: Rash (occurs after a delay of 2–8 weeks), syndrome of inappropriate antidiuretic hormone release, aplastic anemia, thrombocytopenia, anemia, leukopenia, hyponatremia
iv. Extended-release tablets (Tegretol XR) 100, 200, and 400 mg; extended-release capsules (Carbatrol) 100, 200, and 300 mg available. Dosing is still twice daily. Do not crush or chew. Extended-release capsules (Carbatrol) can be opened and sprinkled on food. Ghost tablets can occur in the stool with the extended-release tablets (Tegretol XR).
v. Patients with the *HLA-B*1502* allele are at a 10-fold elevated risk of Stevens-Johnson syndrome.
(a) Testing is recommended for Asians (including Indians).
(b) More than 15% of populations in Hong Kong, Malaysia, the Philippines, and Thailand have this allele.
vi. Patients with the *HLA-A*3101* allele are also at a 12-fold elevated risk of hypersensitivity syndrome and a 3-fold elevated risk of maculopapular exanthema.
(a) Prevalence of this allele is 2%–5% in northern European populations and 9.1% in Japanese populations.
(b) No recommendations have been issued for testing for this allele.
vii. Nonepileptic indication: Trigeminal neuralgia

e. Cenobamate (Xcopri)
i. Mechanism of action: Inhibits voltage-gated sodium channels, modulates GABA receptors
ii. Use slow dose titration because of DRESS (drug rash with eosinophilia and systemic symptoms).
iii. Contraindications: Familial short QT syndrome

iv. Adjust dosing with renal function.
v. CYP3A4 inducer; CYP2C19 inhibitor
vi. Schedule V

f. Eslicarbazepine acetate (Aptiom)
i. Mechanism of action: Fast sodium channel blocker
ii. Prodrug for eslicarbazepine, with active metabolites; *R*-licarbazepine 5%, oxcarbazepine 1%
iii. Adverse effects: Similar to those of carbamazepine; possibly reduced risk of rash, aplastic anemia, thrombocytopenia, and leukopenia
iv. Adjust dose if creatinine clearance (CrCl) is less than 50 mL/minute/1.73 m^2.

g. Ethosuximide (Zarontin)
i. Mechanism of action: T-type calcium current blocker
ii. Useful only for absence seizures
iii. Adverse effects: Anorexia, gastric upset, nausea, vomiting, epigastric/abdominal pain, drowsiness, leukopenia, agranulocytosis, pancytopenia

h. Everolimus (Afinitor)
i. Indicated for seizures caused by tuberous sclerosis
ii. Mechanism of action: Kinase inhibitor
iii. Titrate dose to achieve a trough whole blood concentration of 5–15 ng/mL. Monitor concentrations every 1–2 weeks during dose titration and dose adjustments. Monitor concentrations every 2 weeks when adding and discontinuing a strong P-glycoprotein (P-gp) or CYP3A4 inducer or inhibitor. Measure concentrations every 3 months on a stable dose with changing body surface area. Measure concentrations every 6–12 months with a stable dose and body surface area.
iv. Reduce dose in severe (Child-Pugh class C) hepatic failure

i. Felbamate (Felbatol)
i. Mechanism of action: Blocks glycine site on *N*-methyl-D-aspartate receptor
ii. Serious adverse effects: Hepatotoxicity, aplastic anemia. Patient or guardian must sign consent form.
iii. Uses: Only when seizures are severe and refractory to other medications and when the benefit clearly outweighs the potential adverse effects

j. Fenfluramine (Fintepla)
i. Mechanism of action for seizures: Unknown
ii. Indication: Seizures caused by Dravet syndrome in individuals older than 2 years
ii. Contraindications: Valvular heart disease, pulmonary arterial hypertension
iii. Only available through REMS (Risk Evaluation and Mitigation Strategies) program
iv. Increased risk of serotonin syndrome in combination with other serotonergic drugs

k. Fosphenytoin (Cerebyx)
i. Mechanism of action: Prodrug for phenytoin; fast sodium channel blocker
ii. Uses: Parenteral formulation for loading or maintenance dosing in place of phenytoin; status epilepticus
iii. Pharmacokinetics: Enzyme inducer, nonlinear kinetics
iv. Dosing: Phenytoin equivalents (PE) (1.5 mg of fosphenytoin is equivalent to 1 mg of phenytoin sodium or 1 PE) are used. Loading dose: 10–20 mg of phenytoin sodium equivalents (PE)/kg intravenous or intramuscular dosing is appropriate. Maintenance dosage: Begin with 4–6 mg PE/kg/day in divided doses after administration of the loading dose.
v. Adverse effects: Hypotension, perianal itching, other adverse effects of phenytoin
vi. Advantages over phenytoin
(a) Intramuscular or intravenous dosing
(b) Phlebitis is minimized.

(c) Infusion can be up to 150 mg PE per minute. In status epilepticus, infusion should be at 100–150 mg PE per minute. Maximum infusion rate is not to exceed 150 mg PE per minute.
(d) Can deliver in normal saline solution or D_5W (5% dextrose [in water] injection)

l. Gabapentin (Neurontin)
i. Mechanism of action: Inhibition of α2δ subunit of voltage-dependent calcium channels
ii. Pharmacokinetics: Not metabolized, eliminated renally; adjustments may be necessary for renal dysfunction and hemodialysis
iii. Nonepileptic indication: Postherpetic neuralgia pain
iv. Doses often exceed product information maximum of 3600 mg/day.
v. Extended-release tablets (Gralise) 300 and 600 mg are available. Their indication is for postherpetic neuralgia, not epilepsy.
vi. Gabapentin enacarbil (Horizant) extended-release tablets 300 and 600 mg are available. This agent is a prodrug for gabapentin and is indicated for postherpetic neuralgia and restless legs syndrome, not epilepsy.
vii. Increased risk of sedation and respiratory depression when used in combination with other sedating medications or opioids.

m. Lacosamide (Vimpat)
i. Mechanism of action: Slow sodium channel blocker
ii. Maximum dose is 300 mg/day with a CrCl of 30 mL/minute/1.73 m^2 or less or with mild to moderate hepatic impairment.
iii. Adverse effects: PR interval prolongation or first-degree atrioventricular block; baseline and steady-state electrocardiogram (ECG) recommended in patients with known cardiac conduction problems, taking medications known to induce PR interval prolongation, or with severe cardiac disease
iv. Controlled substance scheduled C-V because of euphoric effects
v. Parenteral formulation: Has an FDA indication only for replacement of oral formulation

n. Lamotrigine (Lamictal)
i. Mechanism of action: Decreases glutamate and aspartate release, delays repetitive firing of neurons, blocks fast sodium channels
ii. Adverse effects: Rash is a primary concern because of concern for progression to Stevens-Johnson syndrome or toxic epidermal necrolysis; lamotrigine must be titrated slowly to avoid a rash.
iii. Valproic acid decreases lamotrigine metabolism (increases the serum concentration of lamotrigine); this interaction requires even slower titration and lower final doses.
iv. Estrogen-containing oral contraceptives increase lamotrigine clearance, so twice the amount of lamotrigine may be necessary.
v. Extended-release tablets (Lamictal XR) are available (25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg).
vi. Nonepileptic indications: Maintenance treatment of type I bipolar disorder

o. Levetiracetam (Keppra)
i. Mechanism of action: May prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity through binding at SV2A receptor
ii. Pharmacokinetics: Not metabolized extensively; adjust dose in renal dysfunction; no drug interactions with other seizure medications
iii. Adverse effects: Drowsiness, behavioral changes, depression, agitation
iv. Parenteral use: Currently FDA indicated only for replacement of oral dosing; however, may be used for status epilepticus
v. Extended-release tablets (500 mg, 750 mg) are available for once-daily dosing.

p. Oxcarbazepine (Trileptal)
    i. Mechanism of action: Fast sodium channel blocker
    ii. Pharmacokinetics: Active metabolite 10-monohydroxy oxcarbazepine; enzyme inducer, no autoinduction
    iii. Drug interactions: Enzyme inducer, decreases effectiveness of hormonal contraceptives
    iv. Adverse effects: Hyponatremia more common than with carbamazepine (increased dose and increased age increase risk of hyponatremia); blood dyscrasias less common than with carbamazepine; 25%–30% of patients with hypersensitivity to carbamazepine will have hypersensitivity to oxcarbazepine; rash
    v. Extended-release tablets (Oxtellar XR) are available (150 mg, 300 mg, 600 mg).
q. Perampanel (Fycompa)
    i. Mechanism of action: Noncompetitive antagonist of the inotropic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor
    ii. Pharmacokinetics: 95%–96% protein bound to albumin and α_1-acid glycoprotein; metabolized by CYP 3A4 and 3A5; 105-hour half-life
    iii. Adverse effects: Neuropsychiatric effects (irritability, aggression, anger, anxiety), dizziness, gait disturbance, weight gain
    iv. Perampanel is a schedule III controlled substance.
r. Phenobarbital (Luminal)
    i. Mechanism of action: Increases GABA-mediated chloride influx
    ii. Pharmacokinetics: Enzyme inducer
    iii. Adverse effects: Hyperactivity, cognitive impairment
    iv. Phenobarbital is a schedule IV controlled substance.
    v. Nonepileptic use: Anxiety, severe alcohol withdrawal
s. Phenytoin (Dilantin, Phenytek)
    i. Mechanism of action: Fast sodium channel blocker
    ii. Pharmacokinetics: Enzyme inducer, nonlinear kinetics
    iii. Administration considerations
        (a) Intravenous formulation: Very basic product. Phlebitis and extravasation are concerns; hypotension; maximal infusion rate of 50 mg/minute because of risk of cardiac arrhythmias and hypotension. Can prepare only in normal saline solution
        (b) Oral suspension: Must be shaken well; adheres to feeding tubes and is bound by enteral nutrition products
    iv. Dose-related adverse effects: Nystagmus, ataxia, drowsiness, cognitive impairment
    v. Non-dose-related adverse effects: Gingival hyperplasia, hirsutism, acne, rash, hepatotoxicity, coarsening of facial features
t. Pregabalin (Lyrica)
    i. Mechanism of action: Inhibition of α2δ subunit of voltage-dependent calcium channels
    ii. Pharmacokinetics: Not metabolized, renally excreted; reduce dose in renal dysfunction
    iii. Adverse effects: Drowsiness, blurred vision, weight gain, edema, angioedema, creatine kinase elevations (three reports of rhabdomyolysis), rash
    iv. Schedule V controlled substance: Insomnia, nausea, headache, diarrhea reported after abrupt discontinuation; gradually discontinue over at least 1 week
    v. Nonepileptic indications: Neuropathic pain associated with diabetic neuropathy, postherpetic neuralgia, spinal cord injury, and fibromyalgia
    vi. Increased risk of sedation and respiratory depression when used in combination with other sedating medications or opioids

Table 1. Medication Selection for Various Seizure Types[a]

Drug	Focal	Generalized Motor	Absence	Atonic	Myoclonic	Infantile Spasms	Dravet Syndrome	Lennox-Gastaut Syndrome
Brivaracetam	3	—	—	—	—	—	—	—
Cannabidiol	—	—	—	—	—	—	3	3
Carbamazepine	1	1	—	4	4	—	—	—
Cenobamate	4	—	—	—	—	—	—	—
Clobazam	4	4	3	—	3	—	2	1
Clonazepam	3	3	2	1	2	2	—	1
Diazepam	—	—	—	—	4	4	—	2
Eslicarbazepine	4	—	—	—	—	—	—	—
Ethosuximide	—	—	1	—	4	—	—	—
Felbamate	5	5	5	—	5	—	—	5
Fenfluramine	—	—	—	—	—	—	5	—
Gabapentin	1	2	—	—	—	—	—	—
Lacosamide	1	—	—	—	—	—	—	—
Lamotrigine	1	1	2	3	3	—	—	1
Levetiracetam	1	1	4	—	3	—	1	—
Lorazepam	3	3	3	—	3	—	—	—
Oxcarbazepine	1	1	—	3	3	—	—	—
Perampanel	4	—	—	—	—	—	—	—
Phenobarbital	2	2	2	—	3	—	—	—
Phenytoin	2	2	—	—	3	—	—	—
Pregabalin	4	—	—	—	—	—	—	—
Primidone	2	2	2	—	—	—	—	—
Rufinamide	4	3	3	3	—	—	—	1
Stiripentol	—	—	—	—	—	—	4	—
Tiagabine	4	—	—	4	4	—	—	—
Topiramate	1	1	3	3	1	—	—	—
Valproic acid	2	1	1	1	1	1	2	—
Vigabatrin	5	5	—	—	—	5	—	—
Zonisamide	1	3	3	—	4	—	—	—

[a]Not all uses are FDA-approved indications. 1 = first-line drug; 2 = second-line drug; 3 = some therapeutic effect; 4 = adjunctive therapy; 5 = used only when benefits outweigh risks; 6 = in combination with clobazam.

Table 2. Selected Interactions Between Seizure Medications

Antiepileptic Drug	Added Seizure Medication	Change in Serum Concentration of the Initial Seizure Medication	Mechanism
Brivaracetam	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
	Ethosuximide	Decreased	Increased metabolism
Carbamazepine	Brivaracetam	Increased epoxide (active component of carbamazepine)	Inhibits epoxide degradation
	Cenobamate	Decreased	Increased metabolism
	Felbamate	Decreased, increased epoxide (active component of carbamazepine)	Inhibits epoxide degradation
	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
	Primidone	Decreased	Increased metabolism
	Rufinamide	Decreased	Increased metabolism
	Eslicarbazepine	Increased	Decreased metabolism
Clobazam	Carbamazepine	Decreased	Increased metabolism
	Cannabidiol	Increased *N*-desmethylclobazam (active metabolite)	Decreased metabolism
	Cenobamate	Increased N-desmethylclobazam (active metabolite)	Decreased metabolism
	Stiripentol	Increase in clobazam and *N*-desmethylclobazam (active metabolite)	Decreased metabolism
Eslicarbazepine	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
	Carbamazepine	Decreased	Probable increased metabolism
Everolimus	Cannabidiol	Increased	Decreased metabolism
Felbamate	Phenytoin	Decreased	Increased metabolism
	Carbamazepine	Decreased	Increased metabolism
Fenfluramine	Stiripentol	Increase fenfluramine and decrease norfenfluramine (active metabolite)	Decreased metabolism
Lamotrigine	Cenobamate	Decreased	Increased metabolism
	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
	Primidone	Decreased	Increased metabolism
	Rufinamide	Decreased	Increased metabolism
	Valproic acid	Increased	Decreased metabolism
	Carbamazepine	Decreased	Increased metabolism
Oxcarbazepine	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
	Valproic acid	Decreased	Unknown
	Carbamazepine	Decreased	Increased metabolism

Table 2. Selected Interactions Between Seizure Medications *(continued)*

Antiepileptic Drug	Added Seizure Medication	Change in Serum Concentration of the Initial Seizure Medication	Mechanism
Perampanel	Oxcarbazepine	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
	Oxcarbazepine	Increased	Decreased metabolism
Phenobarbital	Cenobamate	Increased	Decreased metabolism
	Phenytoin	Increased	Unknown
	Rufinamide	Increased	Decreased metabolism
	Valproic acid	Increased	Inhibition of metabolism
Phenytoin	Brivaracetam	Increased	Unknown, only with brivaracetam doses ≥ 400 mg/day
	Carbamazepine	Decreased	Increased metabolism
	Eslicarbazepine	Increased	Decreased metabolism
	Oxcarbazepine	Increased or no change	Unknown
	Phenobarbital	Increased or decreased	Decreased or increased metabolism
	Rufinamide	Increased	Unknown
	Topiramate	Increased	Decreased metabolism
	Valproic acid	Decreased total; increased free	Displacement from binding sites
	Vigabatrin	Decreased	Increased metabolism
Primidone	Carbamazepine	Increased phenobarbital concentration	Unknown
	Cenobamate	Increased phenobarbital concentration	Decreased metabolism
	Phenytoin	Increased phenobarbital concentration	Unknown
Rufinamide	Carbamazepine	Decreased	Increased metabolism
	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
	Primidone	Decreased	Increased metabolism
	Valproic acid	Increased	Decreased clearance
Stiripentol	Rifampin	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
	Phenobarbital	Decreased	Increased metabolism
	Carbamazepine	Decreased	Increased metabolism
	Oxcarbazepine	Decreased	Increased metabolism
Topiramate	Carbamazepine	Decreased	Increased metabolism
	Lamotrigine	Decreased	Unknown
	Phenytoin	Decreased	Increased metabolism
	Valproic acid	Decreased	Increased metabolism

Table 2. Selected Interactions Between Seizure Medications *(continued)*

Antiepileptic Drug	Added Seizure Medication	Change in Serum Concentration of the Initial Seizure Medication	Mechanism
Valproic acid	Carbamazepine	Decreased	Increased metabolism
	Felbamate	Increased	Unknown
	Oxcarbazepine	Decreased	Unknown
	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism
	Primidone	Decreased	Increased metabolism
	Topiramate	Decreased	Increased metabolism
Zonisamide	Carbamazepine	Decreased	Increased metabolism
	Phenobarbital	Decreased	Increased metabolism
	Phenytoin	Decreased	Increased metabolism

Table 3. Selected Interactions of Non-ASMs on Seizure Medications

Seizure Medication	Other Drug	Effect on the Seizure Medication	Mechanism
Carbamazepine	Cimetidine	Increased serum concentration	Inhibition of carbamazepine metabolism
	Diltiazem	Increased serum concentration	Inhibition of carbamazepine metabolism
	Erythromycin	Increased serum concentration	Inhibition of carbamazepine metabolism
	Isoniazid	Increased serum concentration	Inhibition of carbamazepine metabolism
	Nefazodone	Increased serum concentration	Inhibition of carbamazepine metabolism
	Theophylline	Decreased serum concentration	Increased carbamazepine metabolism
	Verapamil	Increased serum concentration	Inhibition of carbamazepine metabolism
Clobazam	Fluconazole	Increased serum concentration	Inhibitor of CYP2C19
	Fluvoxamine	Increased serum concentration	Inhibitor of CYP2C19
	Omeprazole	Increased serum concentration	Inhibitor of CYP2C19
Gabapentin	Antacids	Decreased serum concentration	Decreased bioavailability
Lamotrigine	Estrogen-containing contraceptives	Decreased serum concentration	Possibly induction of glucuronidation of lamotrigine
	Rifampin	Decreased serum concentration	Possibly induction of glucuronidation of lamotrigine
Perampanel	Ethanol and other CNS depressants	CNS additive or supra-additive effects	Additive CNS depression
	Rifampin	Decreased serum concentration	Increased metabolism
	St. John's wort	Decreased serum concentration	Increased metabolism

Table 3. Selected Interactions of Non-ASMs on Seizure Medications *(continued)*

Seizure Medication	Other Drug	Effect on the Seizure Medication	Mechanism
Phenobarbital; primidone	Ethanol	Acute ethanol ingestion may cause CNS additive effects and respiratory depression; chronic ethanol ingestion may result in variable effects	Additive CNS depression and decreased barbiturate metabolism with acute ethanol ingestion
Phenytoin	Anticoagulants, oral	May increase phenytoin serum concentration; decreased or increased anticoagulant effects	Complex mechanism
	Antineoplastics (bleomycin, cisplatin, vinblastine, methotrexate, carmustine)	Decreased pharmacologic effect	Unknown, possible decreased absorption caused by antineoplastic mucosal damage
	Chloramphenicol	Increased phenytoin serum concentration; decreased or increased chloramphenicol serum concentration	Inhibition of phenytoin metabolism; effect on chloramphenicol unknown
	Cimetidine	Increased serum concentration	Inhibition of phenytoin metabolism
	Diazoxide	Decreased pharmacologic effect; decreased serum concentration	Increased phenytoin metabolism
	Diltiazem	Increased serum concentration	Inhibition of phenytoin metabolism
	Disulfiram	Increased serum concentration	Inhibition of phenytoin metabolism
	Folic acid	Decreased serum concentration	Complex mechanism
	Isoniazid	Increased serum concentration	Inhibition of phenytoin metabolism
	Phenylbutazone	Increased serum concentration	Inhibition of phenytoin metabolism; plasma protein displacement
	Rifampin	Decreased serum concentration	Increased phenytoin metabolism
	Sulfonamides	Increased serum concentration	Inhibition of phenytoin metabolism
	Trimethoprim	Increased serum concentration	Inhibition of phenytoin metabolism
Topiramate	Hydrochlorothiazide	Increased serum concentration	Unknown
Valproic acid	Estrogen-containing oral contraceptives	Decreased serum concentration	Possibly induction of glucuronidation of lamotrigine
	Meropenem	Decreased serum concentration	Increased valproic acid metabolism
	Rifampin	Decreased serum concentration	Increased valproic acid metabolism
	Salicylates	Increased pharmacologic effect	Plasma protein displacement; increased free valproic concentration

ASM = antiseizure medication; CNS = central nervous system.

Table 4. Pharmacokinetic Parameters of Seizure Medications When Used as Monotherapy

Drug	Therapeutic Serum Concentration (mcg/mL)	Bioavailability (%)	Plasma Protein Binding (%)	Vd (L/kg)	Eliminated Unchanged (%)	Clinically Active Metabolites	Half-life (hr)
Brivaracetam	Not established	> 90	< 20	0.5	< 10	None	9
Cannabidiol	Not established	< 20, significantly increased with fatty meal	> 94	232–535	Little, if any	7-hydroxy-cannabidiol	56–61
Carbamazepine	4–12	> 70	40–90	0.8–1.9 1.5 (neonates) 1.9 (children)	Little, if any	10,11-epoxide	12–17 8–14 (children)
Cenobamate	Not established	85–90	60	0.5–0.7	< 10	None	50–60
Clobazam	Not established	100	80–90	100	3	*N*-desmethylclobazam	36–2 71–82 (*N*-desmethylclobazam)
Clonazepam	20–80 ng/mL	100	47–80	3.2	Low percentage	7-amino, low activity	19–50 22–33 (children)
Eslicarbazepine	Not established	90	< 40	0.87	90	*R*-licarbazepine, oxcarbazepine	13–20
Ethosuximide	40–100	100	0	0.6–0.7	10–20	None	52–60 24–36 (children)
Everolimus	0.005–0.015	Variable	74	Varies depending on dose	< 5	None	~30
Felbamate	30–60[a]	> 90	22–36	0.74–0.85	40–50	None	11–20 13–23 (children)
Fenfluramine	Not established	68–74	50	12	< 25	Norfenfluramine	20
Gabapentin	2–20[a]	Dose-dependent	< 3	0.65–1.04	75–80	None	5–7
Lacosamide	Not established	100	< 15	0.6	40	None	13
Lamotrigine	1–13	98	55	0.9–1.2	10	None	12–55 24–30 (children)
Levetiracetam	12–46[a]	100	< 10	0.5–0.7	66	None	7 5 (children)
Oxcarbazepine	3–35[a]	100[b]	67	0.7	< 1	10-monohydroxy	9[b]
Perampanel	Not established	100	95–96	—	20–36	None	105
Phenobarbital	15–40	80–100	40–60	0.7–1	25	None	80–100 45–173 (neonates) 37–73 (children)
Phenytoin	10–20	85–95	> 90	0.6–0.8	< 5	None	~20[c] 10–140 (neonates)[c] 5–18 (children)[c]
Pregabalin	Not established	≥ 90	0	0.5	90	None	6
Primidone	4–12 (20)[d]	90–100	80	0.6	20–40	Phenobarbital PEMA	10–15; 17 (PEMA) 4.5–18 (children) 10–36 (PEMA; children)
Rufinamide	Not established	85	34	50[e]	2	None	6–10
Stiripentol	Not established	Not determined	99	3.2	< 10	None	4.5–13; increases with increasing dose
Tiagabine	0.02–0.2[a]	90–95	96	1.2	—	None	3.2–5.7
Topiramate	5–20[a]	80	13–17	0.6–0.8	70	None	12–21
Valproic acid	40–100 (150)[d]	100	> 90[f]	0.2	< 5	Unknown	8–17 4–14 (children)
Vigabatrin	Not established	100	0	1.1	80	None	7.5 5.7 (infants)
Zonisamide	10–40	50	40	1.45	35	None	63

[a]Therapeutic serum concentrations not well established.

[b]Bioavailability decreased in children < 8 yr and in older adults; clearance is 80% higher in children 2–4 yr and 40% higher in children 4–12 yr than in adults.

[c]Michaelis-Menten pharmacokinetics; half-life varies with serum concentration; therefore, it might be better to express phenytoin elimination in the length of time it takes to clear 50% of the drug from the body, for example.

[d]Upper end of the serum concentration range is not definitely established.

[e]Depends on dose.

[f]May vary with serum concentration.

NAMR = *N*-acetyl metabolite of ezogabine; PEMA = phenylethylmalonamide; Vd = volume of (drug) distribution.

u. Primidone (Mysoline)
   i. Mechanism of action: Increases GABA-mediated chloride influx
   ii. Metabolized to phenobarbital and phenylethylmalonamide
   iii. Adverse effects: Sedation, drowsiness, ataxia, rash
   iv. Primidone, phenobarbital, and phenylethylmalonamide all have antiepileptic action.
   v. Pharmacokinetics: Enzyme inducer
   vi. Also used for essential tremor
v. Rufinamide (Banzel)
   i. Mechanism of action: Fast sodium channel blocker
   ii. Pharmacokinetics: Absorption increased by food (should be administered with food); metabolized by hydrolysis rather than through CYP enzymes
   iii. Adverse effects: Headache, dizziness, fatigue, somnolence, nausea
   iv. Decreases concentrations of ethinyl estradiol and norethindrone
   v. Has an FDA indication only for Lennox-Gastaut syndrome
   vi. Slightly shortens the QT interval and therefore should not be used in patients with familial short QT syndrome
   vii. Available as an oral solution
w. Stiripentol (Diacomit)
   i. Indicated for Dravet syndrome in combination with clobazam
   ii. Dose: 50 mg/kg/day in two or three divided doses
   iii. Adverse effects: Somnolence, decreased appetite, agitation, ataxia, weight decrease, hypotonia, nausea, tremor, dysarthria, insomnia
   iv. Pharmacokinetics: Inhibits CYP 1A2, 2C19, 2D6, and 3A4
x. Tiagabine (Gabitril)
   i. Mechanism of action: Blocks GABA reuptake in the presynaptic neuron
   ii. Associated with new-onset seizures and status epilepticus in patients without epilepsy
   iii. Adverse effects: Dizziness, asthenia, somnolence, nervousness, tremor, diarrhea
y. Topiramate (Topamax)
   i. Mechanism of action: Fast sodium channel blocker, enhances GABA activity and antagonizes AMPA/kainate activity, weak carbonic anhydrase inhibitor
   ii. Pharmacokinetics: Not extensively metabolized, eliminated in urine
   iii. Adverse effects: Drowsiness, paresthesias, psychomotor slowing (titrate slowly), weight loss, renal stones, acute-angle closure glaucoma, metabolic acidosis, and hyperthermia (associated with decreased perspiration, or oligohidrosis), decreased cognition including word-finding difficulties
   iv. Extended-release formulations (Trokendi XR, Qudexy XR)
   v. Nonepileptic indication: Prophylaxis of migraine headaches
z. Valproic acid, divalproex sodium, valproate (Depacon, Depakene, Depakote, Stavzor)
   i. Mechanism of action: Blocks T-type calcium currents, blocks sodium channels, increases GABA production
   ii. Pharmacokinetics: Enzyme inhibitor
   iii. Parenteral use: Has FDA indication only for replacement of oral dosing; however, sometimes used for status epilepticus, especially if absence status epilepticus
   iv. Adverse effects: Hepatotoxicity, nausea and vomiting, weight gain, interference with platelet aggregation, pancreatitis, alopecia, tremor

v. Available in immediate-release (valproic acid [Depakene]) capsules for three- or four-times-daily dosing; delayed-release (enteric coated) (divalproex sodium [Depakote], valproic acid [Stavzor]) capsules and tablets for twice-daily dosing (if patient taking an enzyme inducer, drug is dosed more often); and extended-release (divalproex sodium [Depakote ER]) tablets for once-daily dosing
vi. Nonepileptic indications: Manic episodes associated with bipolar disorder, prophylaxis of migraine headaches

aa. Vigabatrin (Sabril)
i. Mechanism of action: Irreversible inhibition of GABA transaminase
ii. Pharmacokinetics: Induces CYP2C9; renal elimination; dose adjustment required for CrCl less than 60 mL/minute/1.73 m^2
iii. Adverse effects: Fatigue, somnolence, nystagmus, tremor, blurred vision, vision impairment, weight gain, arthralgia, abnormal coordination, and confusional state
iv. Serious adverse effect: Vision loss; increased risk with higher total dose and duration; periodic vision testing necessary; restricted distribution program; only used for refractory complex partial seizures and infantile spasms
v. Available as oral powder for solution

bb. Zonisamide (Zonegran)
i. Mechanism of action: Fast sodium channel blocker, blocks T-type calcium currents, weak carbonic anhydrase inhibitor
ii. Non-arylamine sulfonamide: Avoid in sulfa-sensitive patients; sometimes used in patients with nonserious sulfa allergies, particularly when non-acrylamides (i.e., sulfonylureas) have been used successfully
iii. Pharmacokinetics: Long half-life, renal elimination
iv. Adverse effects: Depression, rash, psychomotor slowing, paresthesias, kidney stones, blood dyscrasias, hyperthermia (associated with decreased perspiration, or oligohidrosis), metabolic acidosis

Table 5. Starting and Maximal Adult Seizure Medication Doses

Drug	Starting Dose	Usual Maximal Dose
Brivaracetam	50 mg twice daily	200 mg/day
Cannabidiol	2.5 mg/kg twice daily	10 mg/kg twice daily
Carbamazepine	200 mg twice daily	1600 mg/day
Cenobamate	12.5 mg/day	400 mg/day
Clobazam	10 mg/day	40 mg/day
Clonazepam	0.5 mg three times/day	20 mg/day
Eslicarbazepine	400 mg/day	1200 mg/day
Ethosuximide	250 mg twice daily	1.5 g/day
Everolimus	5 mg/m^2	Adjusted to concentrations
Felbamate	400 mg three times/day	3600 mg/day
Fenfluramine	0.1 mg/kg twice daily	0.35 mg/kg twice daily to maximum of 26 mg/day; with stiripentol, 0.2 mg/kg twice daily to maximum of 17 mg/day
Gabapentin	300 mg three times/day	3600 mg/day
Lacosamide	50 mg twice daily	400 mg/day

Table 5. Starting and Maximal Adult Seizure Medication Doses *(continued)*

Drug	Starting Dose	Usual Maximal Dose
Lamotrigine	With valproic acid: 25 mg every other day Without carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid: 25 mg/day With carbamazepine, phenytoin, phenobarbital, or primidone and not with valproic acid: 50 mg/day	With valproic acid: 200 mg/day Without carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid: 375 mg/day With carbamazepine, phenytoin, phenobarbital, or primidone and not with valproic acid: 500 mg/day
Levetiracetam	500 mg twice daily	3000 mg/day
Oxcarbazepine	300 mg twice daily	2400 mg/day
Perampanel	With enzyme-inducing seizure medications: 4 mg/day Without enzyme-inducing seizure medications: 2 mg/day	With enzyme-inducing seizure medications: 12 mg/day Without enzyme-inducing seizure medications: 8 mg/day
Phenobarbital	1–3 mg/kg/day	300 mg/day
Phenytoin	100 mg three times/day	600 mg/day
Pregabalin	75 mg twice daily	600 mg/day
Primidone	100 mg at bedtime	2000 mg/day
Rufinamide	200–400 mg twice daily	3200 mg/day
Stiripentol	50 mg/kg/day in two or three divided doses; must be given with clobazam	3000 mg/day
Tiagabine	With carbamazepine, phenytoin, primidone, phenobarbital: 4 mg/day Without carbamazepine, phenytoin, primidone, phenobarbital: 2 mg/day	With carbamazepine, phenytoin, primidone, phenobarbital: 56 mg/day
Topiramate	25–50 mg/day	1000 mg/day
Valproic acid	10–15 mg/kg/day	60 mg/kg/day
Vigabatrin	500 mg twice daily	3000 mg/day
Zonisamide	100 mg/day	600 mg/day

2. Surgery: Surgery can sometimes drastically reduce the number of seizures; possible surgical procedures include removal of the seizure focus, corpus callosotomy, or implantation of vagus nerve stimulators.
3. Status epilepticus
    a. Treatment principles
        i. Ascertain ABCs (airway, breathing, and circulation).
        ii. Laboratory values (fingerstick blood glucose, CBC, basic metabolic panel, calcium, magnesium, and seizure medication serum concentrations, if applicable) are sent to determine any reversible causes of status epilepticus.
        iii. If blood glucose is less than 50 mg/dL, administer thiamine 100 mg intravenously followed by dextrose 50%.
        iv. Give an emergency medication to stop the seizure immediately.
        v. Follow with an urgent medication to prevent the recurrence of seizures.
        vi. In general, all drugs for status epilepticus should be given parenterally.
        vii. Neuromuscular-blocking drugs do not stop seizures; they stop only the muscular response to the brain's electrical activity.

b. Emergency medications
    i. Lorazepam: Drug of choice
        (a) Rapid onset (2–3 minutes)
        (b) Dosage 0.1 mg/kg (up to 4 mg/dose) at rate of up to 2 mg/minute; may repeat every 5–10 minutes
    ii. Diazepam
        (a) Rapid onset, short duration
        (b) Dosage 0.15 mg/kg (up to 10 mg/dose) at rate of up to 5 mg/minute. May repeat every 5 minutes
        (c) Rectal gel and intranasal formulations are available.
    iii. Midazolam: Preferred for intramuscular administration
        (a) Rapid onset, short duration
        (b) Dosage 0.2 mg/kg (up to 10 mg/dose). Can be given intramuscularly, intranasally, or buccally
c. Urgent medications
    i. Phenytoin: Dosage 20 mg/kg; administration rate less than 50 mg/minute
    ii. Fosphenytoin: Administration rate less than 150 mg of phenytoin equivalent per minute
    iii. Phenobarbital: Dosage 20 mg/kg at 50–100 mg/minute
    iv. Valproic acid: Dosage 20–40 mg/kg at up to 6 mg/kg/minute; does not have FDA-labeled approval for status epilepticus
    v. Levetiracetam: 20–30 mg/kg over 15 minutes; does not have FDA-labeled approval for status epilepticus
    vi. Lacosamide: 200- to 400-mg bolus over 15 minutes; does not have FDA-labeled approval for status epilepticus
d. Refractory status epilepticus medications
    i. Benzodiazepine-resistant status epilepticus: fosphenytoin=levetiracetam=valproate (N Engl J Med 2019;381:2103-13)
    ii. Pentobarbital: Load 5–15 mg/kg up to 50 mg/minute; follow with a 0.5- to 5-mg/kg/hour infusion.
        (a) May have severe hypotension, necessitating treatment with vasopressors; should have continuous blood pressure measurement
        (b) Must be on ventilator
    iii. Thiopental: Load 2–7 mg/kg up to 50 mg/minute; follow with a 0.5- to 5-mg/kg/hour infusion.
        (a) May have severe hypotension, respiratory depression, cardiac depression
        (b) Must be on ventilator
    iv. Midazolam: Load 0.2-mg/kg infused up to 2 mg/minute; follow with a 0.05- to 2-mg/kg/hour infusion.
        (a) May have hypotension, respiratory depression
        (b) May have tachyphylaxis
    v. Propofol: Load a 1- to 2-mg/kg intravenous bolus for 30–60 seconds; follow with a 20- to 200-mcg/kg/minute infusion.
        (a) Significant source of lipids
        (b) Some reports of seizure exacerbation with propofol
        (c) Must be on ventilator
        (d) PRIS (propofol infusion syndrome) with prolonged administration

4. Special populations
    a. Older adults: Pharmacokinetic changes in older adults that may affect seizure medications include the following:
        i. Carbamazepine: Decreased clearance
        ii. Phenytoin: Decreased protein binding if hypoalbuminemic or in renal failure
        iii. Valproic acid: Decreased protein binding
        iv. Diazepam: Increased half-life
        v. Phenylethylmalonamide (active metabolite of primidone): Decreased clearance if CrCl is decreased
        vi. Lamotrigine: Decreased clearance
        vii. Seizure medications with renal elimination must be adjusted according to the CrCl value.
    b. Women's health
        i. During their reproductive years, women with epilepsy should:
            (a) Take the best drug for their seizure type. Women of childbearing age should not be given valproic acid unless other therapies have failed.
            (b) Be treated with monotherapy, if possible
            (c) Discuss the possible decrease in hormonal contraceptive effectiveness if taking enzyme-inducing medications (Table 6)
            (d) Use folic acid supplementation with no less than 0.4 mg/day
        ii. Three practice guidelines exist regarding epilepsy during pregnancy (relevant material excerpted in the text that follows).
            (a) Avoiding valproic acid monotherapy or polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations, particularly neural tube defects, facial clefts, hypospadias, and poor cognitive outcomes. Valproic acid use has now been associated with lower IQ scores at ages 3 and 4½ (Neurology 2012;78:1207-14).
            (b) To reduce the risk of major congenital malformations and poor cognitive outcomes, avoiding the use of seizure medication polytherapy during pregnancy, if possible, should be considered.
            (c) Limiting the dose of valproic acid (less than 700 mg/day), topiramate, or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of major congenital malformations.
            (d) Avoiding the use of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of cleft palate (phenytoin), posterior cleft palate (carbamazepine), cardiac malformations (phenobarbital), and poor cognitive outcomes (phenytoin, phenobarbital).
            (e) Women with epilepsy taking seizure medications during pregnancy probably have an elevated risk of small-for-gestational-age infants and 1-minute Apgar scores less than 7.
            (f) Monitoring of lamotrigine, carbamazepine, and phenytoin serum concentrations during pregnancy should be considered.
            (g) Having levetiracetam and oxcarbazepine (as the mono-hydroxylated derivative) serum concentrations monitored during pregnancy may be considered.

Table 6. Effect of Seizure Medications on Hormonal Contraceptives

Seizure Medication	Oral Contraceptives, Contraceptive Patch, Contraceptive Vaginal Ring, Progestogen Implant	Medroxyprogesterone Acetate Depot Injection, Levonorgestrel-Releasing Intrauterine System
Carbamazepine Clobazam Eslicarbazepine Felbamate Lamotrigine Oxcarbazepine Perampanel Phenobarbital Phenytoin Primidone Rufinamide Topiramate[a]	Decrease effectiveness	No effect
Benzodiazepines Ethosuximide Gabapentin Lacosamide Levetiracetam Pregabalin Tiagabine Valproic acid Vigabatrin Zonisamide	No effect	No effect

[a]Doses > 200 mg/day.

E. Other Issues
   1. Initiating therapy after a first seizure
      a. Guidance from the American Epilepsy Society and the American Academy of Neurology
      b. Adults with an unprovoked first seizure (e.g., not meningitis, intoxication) will have a 21%–45% chance of having more seizures within the next 2 years. Higher risks are associated with prior brain insults, EEG with epileptiform abnormalities, and nocturnal seizures.
      c. Initiating ASM therapy will probably reduce recurrence risk within the first 2 years but may not increase quality of life.
      d. Initiating ASM therapy early does not change the long-term risk of seizures.
   2. Driving: All states place driving restrictions on people with epilepsy; some require mandatory physician reporting to the state department of transportation.
   3. Medication discontinuation
      a. The following criteria can be used to determine the possibility of withdrawal from ASM therapy:
         i. Patient should be seizure free for 2–5 years on seizure medication.
         ii. Patient should have a single type of focal or generalized tonic-clonic seizures.
         iii. Patient should have a normal neurologic examination and normal IQ.
         iv. Patient's EEG should have become normalized with seizure medication treatment.
      b. If a drug is discontinued, it is usually tapered for several months; a typical regimen would reduce the dose by one-third for 1 month, reduce it by another one-third for 1 month, and then discontinue it.

4. Monitoring
    a. Number of seizures: The goal number of seizures is always zero.
    b. Signs of toxicity
    c. Laboratory values: Specific for each drug
    d. Blood concentrations: Available for many of the medications; commonly used for carbamazepine, phenobarbital, phenytoin, and valproic acid. The International League Against Epilepsy has a position paper on therapeutic drug monitoring, giving situations in which serum concentrations are most likely beneficial:
        i. When a person has attained the desired clinical outcome, to establish an individual therapeutic concentration that can be used subsequently to assess potential causes for a change in drug response
        ii. As an aid in diagnosing clinical toxicity
        iii. To assess adherence, particularly in patients with uncontrolled seizure or breakthrough seizures
        iv. To guide dosage adjustment in situations associated with increased pharmacokinetic variability (e.g., children, older adults, patients with associated diseases, drug formulation changes)
        v. When a potentially important pharmacokinetic change is anticipated (e.g., in pregnancy, or when an interacting drug is added or removed)
        vi. To guide dose adjustments for seizure medications with dose-dependent pharmacokinetics, particularly phenytoin
5. Sexual dysfunction
    a. Described in 30%–60% of men and women with epilepsy
    b. Includes hyposexuality, orgasmic dysfunction, and erectile dysfunction
    c. Mechanism may be induction of CYP isoenzymes to increase testosterone metabolism, increased hepatic synthesis of sex hormone–binding globulin, or induction of aromatase, which converts free testosterone to estradiol.
    d. Sexual dysfunction has been reported with carbamazepine, phenobarbital, phenytoin, pregabalin, topiramate, and zonisamide.
    e. Improved sexual functioning has been reported with lamotrigine and oxcarbazepine.
6. Bone health
    a. Osteopenia or osteoporosis is found in 38%–60% of patients in tertiary epilepsy clinics.
    b. Increased fractures in patients with epilepsy and with seizure medication use
    c. Risk is increased with increased treatment duration; there is a dose-response relationship; the medications most often associated with poor bone health are carbamazepine, clonazepam, phenobarbital, phenytoin, and valproic acid. However, there is now evidence that all seizure medications may contribute to osteopenia or osteoporosis.
    d. Proposed mechanisms: Hepatic induction of CYP isoenzymes leads to increased vitamin D catabolism, impaired calcium absorption, calcitonin deficiency, vitamin K interference, and direct harmful effects on bone cells.
    e. Proposed treatments: High-dose vitamin D (4000 international units/day for adults and 2000 international units/day for children) improves bone mineral density compared with low doses; estrogen may be helpful for women but may also trigger seizures in some women.
7. Suicidality
    a. Meta-analysis of 199 placebo-controlled clinical trials of 11 drugs (n=43,892 patients older than 5 years) showed that patients who received seizure medications had about twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.22%), and there were four completed suicides in the treatment group versus zero in the placebo group.
        i. Risk increased at 1 week and continued through week 24.

ii. Patients with epilepsy (relative risk [RR] 3.6), psychiatric disorders (RR 1.6), or other conditions (RR 2.3) were all at elevated risk of suicidality; no differences between drugs; no differences between age groups

b. The FDA requires a warning and a medication guide for all seizure medications.

c. Recent observational studies show mixed results. When specific ASMs are examined, those most associated with depression and suicidality are levetiracetam, perampanel, phenobarbital, primidone, tiagabine, topiramate, and vigabatrin.

d. A 2013 expert consensus statement made the following points:
   i. Although some (but not all) ASMs can be associated with treatment-emergent psychiatric problems that may lead to suicidal ideation and behavior, the actual suicidal risk has not yet been established; however, it seems to be very low. The risk of discontinuing ASMs or refusing to initiate them is significantly worse and can result in serious harm, including death to the patient.
   ii. Suicidality in epilepsy is multifactorial. Primary operant variables include postictal suicidal ideation; a history of psychiatric disorders, particularly mood and anxiety disorders (and above all, when associated with prior suicidal attempts); and a family history of mood disorder complicated by suicide attempts.
   iii. When initiating or changing ASMs, patients should be advised to report any changes in mood and suicidal ideation.

e. Self-care seizure plans
   i. Train patients and caregivers on first aid for seizures.
   ii. Instruct on when patient should receive emergency care.
   iii. Provide seizure rescue medication (e.g., intranasal diazepam, intranasal midazolam).

Patient Cases

Questions 1–3 pertain to the following case.

T.M. is an 18-year-old woman with newly diagnosed generalized motor myoclonic-type seizures. She is in good health and takes oral contraceptives.

1. Which is the best medication for T.M.'s seizures?
   A. Valproate.
   B. Phenytoin.
   C. Oxcarbazepine.
   D. Levetiracetam.

2. T.M. is concerned about the impact of levetiracetam on her oral contraceptives. Which response is best?
   A. Levetiracetam does not alter the effectiveness of your oral contraceptives.
   B. You should use alternative forms of birth control because levetiracetam decreases oral contraceptive effectiveness.
   C. You may have breakthrough bleeding, but the effectiveness of the oral contraceptive is not changed.
   D. Oral contraceptives decrease the effectiveness of levetiracetam, so you need another form of birth control.

Patient Cases *(continued)*

3. Three months later, T.M.'s seizures are reduced in frequency, but continue. Which would be the best alternative?
   A. Lamotrigine.
   B. Carbamazepine.
   C. Cannabidiol.
   D. Valproate.

4. J.G. is a 34-year-old patient who presents to the emergency department in status epilepticus. All of her laboratory values are normal. Which drug is best to use first?
   A. Valproate.
   B. Lorazepam.
   C. Phenytoin.
   D. Phenobarbital.

5. S.R. is a 37-year-old patient who began taking phenytoin 100 mg 3 capsules orally at bedtime 6 months ago. He has had several seizures since then, the most recent of which occurred 7 days ago. At that time, his phenytoin serum concentration was 8 mcg/mL. The treating physician increased his phenytoin dose to 100 mg 3 capsules orally twice daily. Today, which best represents his expected serum concentration?
   A. 10 mcg/mL.
   B. 14 mcg/mL.
   C. 16 mcg/mL.
   D. 24 mcg/mL.

6. S.S. is a 7-year-old girl. Her teacher contacts the girl's parents because of concern about the girl's "daydreaming" in class. After an evaluation, S.S. is given a diagnosis of generalized, nonmotor (absence) seizures. Which drug is best to treat this type of epilepsy?
   A. Phenytoin.
   B. Valproate.
   C. Carbamazepine.
   D. Ethosuximide.

7. J.B. is a 25-year-old man with a history of seizure disorder. He has been treated with carbamazepine for 1 year, and his current carbamazepine concentration is 12 mcg/mL. Which adverse effect is J.B. most likely to have with carbamazepine at this concentration?
   A. Hepatotoxicity.
   B. Acne.
   C. Gingival hyperplasia.
   D. Diplopia.

Patient Cases *(continued)*

8. M.G. has been prescribed levetiracetam. On which adverse effect is it best to counsel M.G.?
   A. Hepatoxicity.
   B. Renal stones.
   C. Depression.
   D. Word-finding difficulties.

Questions 9 and 10 pertain to the following case.
G.Z., a 26-year-old woman, presents with a 6-month history of "spells." The spells are all the same, and all begin with a feeling in the abdomen that is difficult for her to describe. This feeling rises toward the head. The patient believes that she will then lose awareness. After a neurologic workup, she is given a diagnosis of focal seizures evolving to a bilateral, convulsive seizure. The neurologist is considering initiating either carbamazepine or oxcarbazepine.

9. Which is the most accurate comparison of carbamazepine and oxcarbazepine?
   A. Oxcarbazepine causes more liver enzyme induction than carbamazepine.
   B. Oxcarbazepine does not cause rash.
   C. Oxcarbazepine does not cause hyponatremia.
   D. Oxcarbazepine does not form an epoxide intermediate in its metabolism.

10. When you see G.Z. 6 months later for a follow-up, she tells you she is about 6 weeks pregnant. She has had no seizures since starting oxcarbazepine. Which strategy is best for G.Z.?
   A. Discontinue her seizure medication immediately.
   B. Change her seizure medication to topiramate.
   C. Continue her seizure medication.
   D. Change her seizure medication to lamotrigine.

II. ISCHEMIC STROKE

A. Epidemiology
   1. Updated definitions
      a. Central nervous system (CNS) infarction: Brain, spinal cord, or retinal cell death attributable to ischemia, according to pathologic evidence, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution, *or* clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury, given symptoms persisting for 24 hours or more or until death, and other etiologies excluded
      b. Ischemic stroke: An episode of neurologic dysfunction caused by focal cerebral, spinal, or retinal infarction
   2. Third or fourth most common cause of death in all developed countries
   3. More than 795,000 cases per year in the United States (128,842 deaths)
   4. Most common cause of adult disability
   5. Risk factors
      a. Nonmodifiable
         i. Age: Stroke risk doubles each decade after 55 years.
         ii. Race: Risk for Native Americans is greater than for African Americans, whose risk is greater than for whites.

iii. Sex: Risks are greater for men than for women; however, about half of strokes occur in women.
iv. Low birth weight: Odds of stroke for those with birth weights less than 2500 g are twice has high as the odds for those weighing more than 4000 g.
v. Family history: Parental history increases risk; some coagulopathies (e.g., protein C and S deficiencies, factor V Leiden mutations) are inherited.

b. Somewhat modifiable: Diabetes mellitus increases risk 1.8–6 times; risk reduction has not been shown for glycemic control.
c. Modifiable
i. Hypertension increases risk 1.4–8 times; 32% risk reduction with control
ii. Smoking increases risk 1.9 times; 50% risk reduction in 1 year, baseline risk at 5 years with smoking cessation; exposure to environmental cigarette smoke also increases risk
iii. Oral contraceptives with less than 50 mcg of estrogen double the risk of stroke; those with more than 50 mcg of estrogen have a 4.5 times increased risk; risk increases with age; adding smoking to oral contraceptive use increases risk of stroke 7.2 times; obesity and hypertension also increase the risk with oral contraceptives.
iv. Postmenopausal hormone therapy increases risk 1.4 times.
v. Atrial fibrillation increases risk 2.6–4.5 times; 68% risk reduction with warfarin; direct oral anticoagulants (DOACs) have risk reduction similar to warfarin
vi. Coronary heart disease increases risk 1.55 times (women) to 1.73 times (men).
vii. Asymptomatic carotid stenosis increases risk 2 times; about a 50% risk reduction with endarterectomy
viii. Dyslipidemia: High total cholesterol increases risk 1.5 times; low high-density lipoprotein cholesterol (less than 35 mg/dL) increases risk 2 times; 27%–32% risk reduction with statins in patients with coronary heart disease, hypertension, or diabetes. Twenty-five percent risk reduction with high-dose statins compared with low-dose statins
ix. Obesity (especially abdominal body fat) increases risk 1.75–2.37 times; risk reduction with weight loss is unknown.
x. Physical inactivity increases risk 2.7 times; risk reduction with increased activity is unknown.
xi. Sickle cell disease increases risk 200–400 times; 91% risk reduction with transfusion therapy
xii. Peripheral artery disease increases risk 3 times; impact of risk reduction strategies is unknown.
xiii. Pregnancy increases risk 2.4 times over nonpregnant women; the risk remains elevated for the first 6 weeks postpartum.
xiv. Patent foramen ovale increases the risk of stroke in young patients (younger than 55 years).
xv. Depression increases the risk of stroke 1.35 times compared with nondepressed people.

d. Less well documented: Alcohol abuse (5 or more drinks a day), hyperhomocystinemia, drug abuse (cocaine, amphetamines, and heroin), hypercoagulability, periodontal disease, inflammation and infection, sleep-disordered breathing (sleep apnea and snoring), metabolic syndrome, and migraine with aura

B. Primary Prevention
1. Reduction in risk factors (e.g., control of hypertension, smoking cessation, control of diabetes, cholesterol reduction). Control of hypertension produces the greatest benefit in primary prevention of stroke.
2. Patient education: Patients should be educated about stroke warning signs and instructed to seek emergency care if they have any of them. Warning signs: Sudden numbness or weakness of the face, arm, or leg, especially on one side of the body; sudden confusion; trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking; dizziness, loss of balance or coordination; sudden, severe headache with no known cause

3. Treatment of atrial fibrillation: Up to 70% of cases are inappropriately treated. (For a more detailed discussion, see the chapter on anticoagulation.)
    a. Recommendations are based on the following: Chest 2018;154:1121-201; Neurology 2014;82:716-24; Stroke 2014;45:3754-832.
    b. CHA_2DS_2-VASc is used for risk stratification.
        i. Assign 1 point each for congestive heart failure, hypertension, age 65–74 years, diabetes, vascular disease, or female sex.
        ii. Assign 2 points for previous stroke or transient ischemic attack (TIA) or age 75 or older.
        iii. Total for the CHA_2DS_2-VASc score
            (a) In general, those younger than 65 and with lone atrial fibrillation, irrespective of sex (0 in males, 1 in females), give no therapy.
            (b) If greater than 1 in males or greater than 2 in females, consider treatment with aspirin or oral anticoagulant.
            (c) If 2 or more non–sex-related risk factors, give oral anticoagulant or aspirin and clopidogrel in individuals not candidates for DOACs or warfarin.
    c. Dabigatran (Pradaxa)
        i. When oral anticoagulation is recommended and the patient's bleeding risk is high, current guidelines suggest dabigatran 150 mg twice daily over warfarin (target international normalized ratio [INR] of 2.5). Dabigatran had similar rates of hemorrhage, but intracranial hemorrhage was less likely with dabigatran, and GI hemorrhage was more likely.
        ii. Mechanism of action: Direct thrombin inhibitor
        iii. Dose: 150 mg twice daily; dose reduction needed in severe renal dysfunction
        iv. Dose reduction to 75 mg twice daily is recommended when administered with dronedarone or systemic ketoconazole in patients with a CrCl of 30–50 mL/minute/1.73 m^2.
        v. Avoid the use of dabigatran and P-gp inhibitors in patients with a CrCl of 15–30 mL/minute/1.73 m^2.
        vi. Avoid use in patients with a CrCl less than 15 mL/minute/1.73 m^2 or advanced liver disease.
        vii. Avoid use in patients with mechanical heart valves.
        viii. Capsule should not be opened because it increases bioavailability by 75%. Store in original manufacturer container or blister pack.
        ix. Idarucizumab (Praxbind) is a monoclonal antibody fragment used to reverse dabigatran anticoagulation.
            (a) Specific for dabigatran; can use other anticoagulants to anticoagulate patient, if needed
            (b) Dose is 5 g administered as two rapid 2.5-g intravenous boluses.
            (c) May reinitiate dabigatran in 24 hours
    d. Rivaroxaban (Xarelto) is as effective as warfarin with a similar risk of major bleeding. Higher risk of GI bleeding and lower risk of intracranial hemorrhage and fatal bleeding
        i. Mechanism of action: Direct factor Xa inhibitor
        ii. Dose: 20 mg/day with evening meal; dose reduction needed in renal dysfunction
        iii. Metabolized by CYP3A4/5, CYP2J2, P-gp, and *ABCG2;* avoid concomitant use with strong inhibitors or inducers
        iv. Andexanet alfa reversal agent
    e. Apixaban (Eliquis) is more effective than warfarin, with a lower risk of stroke and lower risk of bleeding and mortality.
        i. Mechanism of action: Direct, competitive factor Xa inhibitor
        ii. Dose: 5 mg twice daily; dose reduction needed in renal dysfunction

iii. Metabolized by CYP3A4 and P-gp; reduce dose if given with inhibitors (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin); avoid with strong inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort)
iv. Andexanet alfa reversal agent

f. Edoxaban (Savaysa) is as effective as warfarin, with a lower risk of bleeding.
i. Mechanism of action: Inhibition of factor Xa, prothrombinase, and thrombin-induced platelet aggregation
ii. Dose: 60 mg/day; reduce dose with CrCl less than 50 mL/minute/1.73 m2
iii. Metabolized by CYP3A4

g. Warfarin (Coumadin) is probably more effective than clopidogrel plus aspirin, but intracranial bleeding is more common.
i. INR range 2–3
ii. Give warfarin if patient has atrial fibrillation and mitral stenosis or prosthetic heart valve.

C. Treatment of Acute Event
1. Heparin
a. Good data on outcomes unavailable; generally not recommended for stroke treatment at therapeutic doses; increases risk of hemorrhagic transformation; heparin is often used for deep venous thrombosis prevention at a dose of 10,000–15,000 units/day given subcutaneously
b. Avoid in hemorrhagic stroke.
2. Streptokinase: Should be avoided because of excess mortality
3. Tissue plasminogen activator (Alteplase)
a. Within 4½ hours of symptom onset
b. Three-month outcome significantly improved (decreased disability)
c. Intracerebral hemorrhage increased but no increase in mortality
d. Dose 0.9 mg/kg intravenously (maximum is 90 mg), with 10% as a bolus and the remainder over 1 hour. The bolus should be administered within 60 minutes of hospital arrival.
e. Antiplatelet agents should be held for 24 hours after tissue plasminogen activator administration.
f. Exclusion criteria
i. Intracranial bleeding (or history) or subarachnoid bleeding
ii. Other active internal bleeding
iii. Intracranial/spinal surgery, head trauma, stroke within 3 months
iv. Major surgery or serious trauma within 2 weeks, if risk of bleeding outweighs the anticipated benefits of reduced stroke-related neurologic deficits
v. Gastrointestinal (GI) hemorrhage within 3 weeks or structural GI malignancy
vi. Blood pressure greater than 185/110 mm Hg. If medications are given to lower blood pressure, blood pressure should be stabilized before beginning treatment and maintained below 180/105 mm Hg for at least the first 24 hours after treatment.
vii. Glucose less than 50 mg/dL or greater than 400 mg/dL, unless subsequently normalized
viii. Arterial puncture at a noncompressible site within 1 week
ix. Intracranial intra-axial neoplasm, arteriovenous malformation, or giant unruptured and unsecured aneurysm
x. INR greater than 1.7, activated partial thromboplastin time greater than 40 seconds, prothrombin time greater than 15 seconds, platelet count less than 100,000 cells/m^3, patients who have received a dose of low-molecular-weight heparin within the previous 24 hours, or patients who have taken direct thrombin inhibitors or direct factor Xa inhibitors in the previous 48 hours
xi. Infective endocarditis
xii. Pregnancy, if the anticipated benefits of treating moderate to severe stroke do not outweigh the anticipated risks of uterine bleeding

xiii. Individuals presenting in the 3- to 4.5-hour window may benefit even if they are older than 80, take warfarin, have a history of diabetes with previous stroke, or have severe stroke symptoms (NIHSS [National Institutes of Health Stroke Scale] score greater than 25).

4. In patients with minor strokes or TIA, dual antiplatelet therapy with aspirin and clopidogrel should be initiated immediately and continued for 21 days.
5. A clot retriever within 24 hours may be useful in select patients with or without prior tissue plasminogen activator.

D. Secondary Prevention
   1. Reduction in all modifiable risk factors (specific changes in the text that follows according to Stroke 2014;45:2160-236)
      a. Hypertension: Goal less than 140/less than 90 mm Hg. With lacunar stroke, may target less than 130 mm Hg systolic
      b. Hyperlipidemia: High-intensity statin therapy should be initiated or continued as first-line therapy in women and men younger than 75 who have had stroke or TIA.
   2. Carotid endarterectomy if 70%–99% stenosis. For 50%–69% stenosis, carotid endarterectomy recommendation depends on age, sex, and comorbidities; use aspirin 50–100 mg/day and statin therapy before and after the procedure.
   3. Carotid angioplasty and stenting may be an alternative to carotid endarterectomy in some patients, particularly younger patients.
   4. Antiplatelet therapy: Dual antiplatelet therapy with aspirin and clopidogrel should be initiated within 24 hours of a minor stroke or TIA and continued for 21 days. After a major stroke, dual antiplatelet therapy with aspirin and clopidogrel should be initiated and continued for 90 days. After these time intervals, therapy should be transitioned to single antiplatelet therapy and continued indefinitely. Each agent has shown efficacy in reducing secondary stroke risk. Guidelines differ slightly on their recommendations. The American Stroke Association suggests that aspirin, aspirin/extended-release dipyridamole, and clopidogrel are all options for ongoing prophylaxis.
      a. Aspirin
         i. Dose: 75–100 mg/day
         ii. If the patient has an additional stroke while taking aspirin, no evidence suggests increasing the aspirin dose will provide additional benefit.
      b. Aspirin/dipyridamole (Aggrenox)
         i. Capsule contains dipyridamole extended-release pellets (200 mg) and aspirin tablet (25 mg).
         ii. Dose: 1 capsule orally twice daily
         iii. Most common adverse effects: Headache, nausea, and dyspepsia; can increase liver enzymes
      c. Clopidogrel (Plavix)
         i. Inhibits adenosine diphosphate–induced platelet aggregation
         ii. Dose: 75 mg/day orally
         iii. Very low incidence of neutropenia (0.04% severe)
         iv. Rarely, thrombotic thrombocytopenic purpura has been reported.
         v. Partly metabolized by CYP2C19; interactions may occur with inhibitors of CYP2C19, notably proton pump inhibitors, or with genetic polymorphisms of this enzyme. The FDA has issued an alert on this topic (www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190787.htm).
      d. Cilostazol (Pletal)
         i. Inhibits cyclic adenosine monophosphate phosphodiesterase type 3–induced platelet aggregation
         ii. Dose: 100 mg orally twice daily on an empty stomach
         iii. Metabolized extensively by CYP3A4 and CYP2C19

iv. Adverse effects: Headache, palpitation, diarrhea, and dizziness; rarely, thrombocytopenia or agranulocytosis. Contraindicated in patients with congestive heart failure
v. Monitoring: CBC with differential every 2 weeks for 3 months; periodically thereafter. Thus, used infrequently

5. Anticoagulation: Warfarin (Athrombin-K, Coumadin, Jantoven, Panwarfin) or direct oral anticoagulants (DOACs) (dabigatran, rivaroxaban, apixaban, edoxaban)
   a. Prevention of second ischemic event, if patient has atrial fibrillation (warfarin or DOACs), rheumatic mitral valve disease (warfarin), mechanical prosthetic heart valves (warfarin), bioprosthetic heart valves (warfarin), or left ventricular mural thrombus formation (warfarin)
   b. Target INR: 2–3 for nonvalvular atrial fibrillation; 2.5–3.5 for mechanical prosthetic heart valves

Patient Cases

Questions 11–13 pertain to the following case.

L.R. is a 78-year-old woman who presents to the emergency department for symptoms of right-sided paralysis. She states that these symptoms began about 6 hours ago and have not improved since then. She also has hypertension, breast cancer, diabetes mellitus, minimal cognitive impairment, and osteoarthritis.

11. Which is the most accurate list of L.R.'s risk factors for stroke?
    A. Breast cancer, age, osteoarthritis.
    B. Sex, diabetes mellitus, osteoarthritis.
    C. Minimal cognitive impairment, diabetes mellitus, age, sex.
    D. Age, diabetes mellitus, hypertension.

12. Which best describes whether L.R. is a candidate for tissue plasminogen activator for the treatment of stroke?
    A. Yes.
    B. No, she is too old.
    C. No, her stroke symptoms began too long ago.
    D. No, her breast cancer is a contraindication for tissue plasminogen activator.

13. L.R. previously took no drugs at home. Which is the best treatment at this time for her?
    A. Metformin and aspirin.
    B. Celecoxib and clopidogrel.
    C. Aspirin and clopidogrel.
    D. Warfarin.

14. As the pharmacist at a community pharmacy, you receive a call from M.W., a 58-year-old man recently given a diagnosis of atrial fibrillation. He is concerned about his risk of a stroke because his friend, who also has atrial fibrillation, asked him which dose of apixaban he is taking. M.W. called you because he is not taking apixaban and wants to know whether he should. He has no other medical conditions and takes atenolol 50 mg/day orally for ventricular rate control. After encouraging M.W. to discuss this with his physician, which best depicts what you should you tell him?
    A. You need apixaban treatment to prevent a stroke.
    B. You do not need apixaban, but you should take aspirin and clopidogrel.
    C. You do not need drug therapy at this time.
    D. Because you have atrial fibrillation, nothing can reduce your risk of stroke.

Patient Cases *(continued)*

13. L.R. previously took no drugs at home. Which is the best treatment at this time for her?
    A. Metformin and aspirin.
    B. Celecoxib and clopidogrel.
    C. Aspirin and clopidogrel.
    D. Warfarin.

14. As the pharmacist at a community pharmacy, you receive a call from M.W., a 58-year-old man recently given a diagnosis of atrial fibrillation. He is concerned about his risk of a stroke because his friend, who also has atrial fibrillation, asked him which dose of apixaban he is taking. M.W. called you because he is not taking apixaban and wants to know whether he should. He has no other medical conditions and takes atenolol 50 mg/day orally for ventricular rate control. After encouraging M.W. to discuss this with his physician, which best depicts what you should you tell him?
    A. You need apixaban treatment to prevent a stroke.
    B. You do not need apixaban, but you should take aspirin and clopidogrel.
    C. You do not need drug therapy at this time.
    D. Because you have atrial fibrillation, nothing can reduce your risk of stroke.

15. L.S. is a 42-year-old woman with a medical history of hypertension, type 2 diabetes, renal failure, and mitral valve replacement. She presents to the anticoagulation clinic for her initial visit. Which best reflects her target INR?
    A. 1.5.
    B. 2.0.
    C. 2.5.
    D. 3.0.

III. PARKINSON DISEASE

A. Epidemiology
    1. Prevalence is 1 million in the United States.
    2. Onset is usually at 40–70 years of age, with peak onset in sixth decade.
    3. Slightly more common in men
    4. Observed in all countries, ethnic groups, and socioeconomic classes

B. Signs and Symptoms
    1. Cardinal signs
        a. Akinesia or hypokinesia
        b. Rigidity
        c. Tremor
        d. Posture or gait abnormalities

2. Secondary signs
    a. Cognitive dysfunction
    b. Autonomic dysfunction
    c. Speech disturbances
    d. Micrographia
    e. Masked facies

C. Treatment
1. General treatment principles
    a. No treatment has unequivocally been shown to prevent the progression of Parkinson disease; therefore, treatment is based on symptoms.
    b. In patients who need the initiation of dopaminergic treatment, either levodopa or a dopamine agonist may be used. Choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with dopamine agonists) for each patient.
    c. Treatment may be initiated with rasagiline as well, but the effects are not robust.
    d. Treatment with several different classes of medications simultaneously is common.
2. Medications
    a. Monoamine oxidase type B (MAO-B) inhibitors
        i. Selegiline (Eldepryl, Zelapar)
            (a) Loses selectivity for MAO-B at doses greater than 10 mg/day
            (b) Contraindicated with meperidine because of serotonin syndrome risk
            (c) Dose: 5 mg orally twice daily (tablets; usually morning and noon); 1.25–2.5 mg/day (orally disintegrating tablets)
            (d) Adverse effects: Nausea, hallucinations, orthostatic hypotension, insomnia (metabolized to amphetamine)
            (e) Dosage forms: Tablets, orally dissolving tablets, and patches. The patches are FDA indicated for depression; they should not usually be used for Parkinson disease.
        ii. Rasagiline (Azilect)
            (a) Selectivity for MAO-B has not been definitively established.
                (1) Contraindicated with meperidine because of serotonin syndrome risk
                (2) Do not administer with tramadol, methadone, dextromethorphan, sympathomimetics, fluoxetine, or fluvoxamine because of serotonin syndrome risk.
                (3) Ciprofloxacin can double the concentration of rasagiline (through CYP1A2 inhibition).
            (b) Dose: 0.5–1 mg/day orally
        iii. Safinamide (Xadago)
            (a) Highly selective MAO-B inhibitor
            (b) Dose 50–100 mg daily
            (c) Reduce dose in hepatic failure (Child-Pugh class C)
            (d) Adverse effects and drug interactions similar to other MAO-B inhibitors
    b. Istradefylline (Nourianz)
        i. Adenosine receptor antagonist
        ii. Adjunct to carbidopa/levodopa
        iii. Treats off-episodes
        iv. Dose: 20 mg daily; may increase to maximum of 40 mg daily
        v. Adverse effects: Dyskinesia, dizziness, constipation, nausea, hallucinations, insomnia
        vi. Drug interactions: CYP3A4 substrate; avoid use with CYP3A4 inducers; maximum dose 20 mg daily with CYP3A4 inhibitors

c. Levodopa inhalation powder (Inbrija)
    i. Treats off-episodes
    ii. Dose: 2 capsules (84 mg) inhaled as needed, up to five times daily
    iii. Adverse effects: Cough, nausea, discolored sputum
d. Carbidopa
    i. Combined in fixed ratios with levodopa
    ii. Prevents some of the peripheral conversion of levodopa to dopamine by inhibiting peripheral dopamine decarboxylase; therefore, levodopa is available to cross the blood-brain barrier
    iii. 75 mg/day is usually needed to inhibit peripheral decarboxylase activity.
e. Carbidopa/levodopa (Parcopa, Sinemet, Duopa, Rytary)
    i. Pharmacokinetic considerations
        (a) High-protein diets decrease absorption.
        (b) Immediate-release half-life 60–90 minutes
        (c) Orally disintegrating tablet available; not absorbed sublingually
        (d) Slow-release considerations: Fewer daily doses; less plasma fluctuations; delay to effect; cannot crush; can divide. No measurable effect on "freezing"
    ii. Acute adverse effects: Nausea and vomiting, orthostatic hypotension, cardiac arrhythmias, confusion, agitation, hallucinations
    iii. Long-term adverse effects: Wearing-off and on-off phenomena, involuntary movements (dyskinesias)
        (a) Wearing-off phenomenon is the return of Parkinson disease symptoms before the next dose. Treatment of wearing-off includes adding a dopamine agonist, adding a MAO-B inhibitor, adding a catechol-*O*-methyl transferase inhibitor, or increasing the frequency or dose of levodopa.
        (b) On-off phenomenon is a profound, unpredictable return of Parkinson disease symptoms without respect to the dosing interval. Treatment of on-off includes adding entacapone, rasagiline, pramipexole, ropinirole, apomorphine, or selegiline or redistributing dietary protein.
        (c) Dyskinesias are drug-induced involuntary movements including chorea and dystonia. Treatment of dyskinesias includes decreasing the levodopa dose or adding amantadine as an antidyskinetic drug.
    iv. Therapy initiation
        (a) Standard formulation: 25 mg/100 mg 1 tablet orally three times daily; also available as orally disintegrating tablet
        (b) Controlled-release formulation: 1 tablet orally two or three times daily
        (c) Titration always necessary
        (d) A combination of formulations may be needed (e.g., ½ tablet of Sinemet 25 mg/100 mg on awakening and 1 tablet of Sinemet CR 25/100 three times daily).
    v. Levodopa may improve disability and mortality.
    vi. Greatest benefit for rigidity and bradykinesia, less benefit for tremor and postural instability
f. Direct dopamine agonists
    i. Drugs: Apomorphine (Apokyn), bromocriptine (Parlodel), pramipexole (Mirapex), ropinirole (Requip), rotigotine (Neupro)
    ii. Bromocriptine is an ergot-derived product: Very rarely, adverse effects such as retroperitoneal, pleuropulmonary, or cardiac fibrosis have been attributed to it; regular ECG monitoring is recommended.
    iii. Rotigotine is a transdermal system. With the initial formulation, problems occurred with crystallization of the medication. The product was withdrawn from the market and has since been reformulated. Rotigotine is currently available.

iv. Dosing: Always titrate to final dose (Table 7).

Table 7. Usual Dosage Range for Dopamine Agonists

Agent	Usual Dosage Range (mg/day)
Bromocriptine	5–40
Pramipexole	1.5–4.5
Ropinirole	0.75–24
Rotigotine	6–8

v. Adverse effects: Nausea, vomiting, postural hypotension, hallucinations, impulsive behaviors (e.g., hypersexuality, gambling, shopping, eating), falling asleep during activities of daily living
vi. Pramipexole and ropinirole also have FDA indications for restless legs syndrome.
vii. Ropinirole and pramipexole are available as extended-release formulations.
viii. Apomorphine: Short-acting dopamine receptor agonist
  (a) Indication: Acute, intermittent treatment of "off" episodes associated with advanced Parkinson disease
  (b) Contraindications: Its use with 5-hydroxytryptamine-3 antagonists (ondansetron, granisetron, dolasetron, palonosetron, and alosetron) causes profound hypotension, sulfite sensitivity, or allergy.
  (c) Pharmacokinetics: When given orally, poorly bioavailable and extensive first-pass metabolism; used as subcutaneous injection in a pen self-injector
  (d) Adverse effects
    (1) Severe nausea and vomiting
      (A) Treat with trimethobenzamide 300 mg three times daily for 3 days before initiating treatment and for at least 6 weeks during treatment.
      (B) About 50% of patients can discontinue trimethobenzamide after 2 months.
      (C) Thirty-one percent of patients had nausea and 11% had vomiting with trimethobenzamide.
    (2) Hypotension
    (3) Hallucinations
    (4) Injection site reactions
    (5) Dyskinesias
  (e) Dosing
    (1) Must be titrated in a setting where blood pressure can be monitored
    (2) In the "off" state, the patient should be given a 0.2-mL (2 mg) test dose.
    (3) Supine and standing blood pressure taken before dose; 20, 40, and 60 minutes after dose
    (4) If tolerated, begin with a 0.2-mL dose as needed; increase by 0.1 mL, if necessary.
    (5) Doses greater than 0.6 mL, more than five times daily, or greater than 20 mg/day have limited experience.
    (6) If first dose is ineffective, do not re-dose.
    (7) If patients do not dose for more than 1 week, reinitiate at a 0.2-mL dose.

g. Anticholinergics
  i. Drugs: Trihexyphenidyl (Artane), benztropine (Cogentin)
  ii. Useful only for tremor

iii. Initial dosing
(a) Trihexyphenidyl 0.5 mg 1 tablet orally twice daily
(b) Benztropine 0.5 mg 1 tablet orally twice daily
iv. Adverse effects: Dry mouth, urinary retention, dry eyes, constipation, confusion

h. Amantadine (Symmetrel)
i. Has symptomatic benefits and may reduce dyskinesias caused by levodopa or dopamine agonists
ii. Dosing: 100 mg 1 tablet orally two or three times daily; caution in renal dysfunction
iii. Adverse effects: Dizziness, insomnia, anxiety, livedo reticularis, nausea, nightmares

i. Catechol-*O*-methyl transferase inhibitors
i. Prevent breakdown of dopamine, more levodopa available to cross blood-brain barrier
ii. Tolcapone (Tasmar): Severely restricted because of hepatotoxicity; must sign consent form
iii. Entacapone (Comtan)
(a) Increased area under the curve, increased half-life; no change in Cmax or Tmax of levodopa
(b) Dosing: 1 tablet with each carbidopa/levodopa dose; maximum of eight times daily; one dosage form (Stalevo) includes carbidopa, levodopa, and entacapone 200 mg
(c) Must use with carbidopa/levodopa
(d) Adverse effects: Dyskinesias, nausea, diarrhea (may be delayed for up to 2 weeks after initiation or dose increase), urine discoloration (orange), hallucinations or vivid dreams
iv. Opicapone (Ongentys)
(a) Dosing: 50 mg daily at bedtime
(b) Take doses 1 hour before or after eating.
(c) Reduce dose by 50% with moderate hepatic failure. Avoid use in severe hepatic failure.

3. Surgery: Several types of surgery are done for Parkinson disease.
a. Thalamotomy: Ablation of portions of the thalamus to control tremor
b. Pallidotomy: Ablation of structures in the globus pallidus for the treatment of Parkinson disease
c. Fetal transplants: Transplantation of dopaminergic tissue into the striatum; considered experimental
d. Trophic factors: Glial-derived nerve growth factor and neurturin have been delivered directly to the striatum or substantia nigra; considered experimental
e. Deep brain stimulation
i. Most common surgery for Parkinson disease
ii. Thought to stimulate areas of the basal ganglia to reversibly block the neuronal activity in the area
iii. Patient selection focuses on patients with
(a) Motor fluctuations or dyskinesias that are not adequately controlled with optimized medical therapy
(b) Medication-refractory tremor
(c) Intolerance of medical therapy
(d) Some centers will not do the surgery in patients older than 70.
iv. Two areas are targeted.
(a) Globus pallidum
(1) Reduces off-time
(2) Reduces dyskinesias
(3) Thought to have fewer cognitive adverse effects than subthalamic nucleus stimulation
(b) Subthalamic nucleus
(1) Reduces off-time
(2) Reduces dyskinesias
(3) Thought to be more effective than globus pallidum stimulation

4. Special situations
    a. Hallucinations or psychosis may be caused by either Parkinson disease or treatment.
        i. Discontinue or reduce Parkinson disease medications as tolerated.
        ii. If an antipsychotic is needed, use quetiapine or clozapine as the first choice.
        iii. Pimavanserin (Nuplazid) FDA approved for Parkinson disease psychotic disorder
        iv. Avoid typical antipsychotics, risperidone, and olanzapine because they may worsen Parkinson symptoms.
    b. Cognitive disorders
        i. Discontinue or reduce Parkinson disease medications as tolerated.
        ii. Rivastigmine (Exelon) has an FDA indication for treatment; other cholinesterase inhibitors may have efficacy.
    c. Sleep disorders, depression, agitation, anxiety, constipation, orthostatic hypotension, seborrhea, blepharitis, and restless legs syndrome can occur in Parkinson disease; treat as usual.

Patient Cases

Questions 16 and 17 pertain to the following case.

L.S. takes carbidopa/levodopa 25 mg/100 mg orally four times daily and trihexyphenidyl 2 mg orally three times daily for Parkinson disease. L.S.'s wife reports that his movements are very slow and that he is having trouble walking.

16. Given these symptoms, which change seems most reasonable?
    A. Increase carbidopa/levodopa, discontinue trihexyphenidyl.
    B. Continue carbidopa/levodopa, increase trihexyphenidyl.
    C. Decrease carbidopa/levodopa, continue trihexyphenidyl.
    D. Decrease carbidopa/levodopa, increase trihexyphenidyl.

17. Six months later, L.S. returns to the clinic concerned that his carbidopa/levodopa dose is wearing off before his next dose is due, because his tremor and slow movements are worse before the next dose of carbidopa/levodopa. Which recommendation is best?
    A. Increase the carbidopa/levodopa dose.
    B. Decrease the carbidopa/levodopa dose.
    C. Increase the dosing interval.
    D. Decrease the dosing interval.

18. P.J. is a 57-year-old man with an 8-year history of Parkinson disease. His current drugs include carbidopa/levodopa 50 mg/200 mg orally four times daily, entacapone 200 mg orally four times daily, and amantadine 100 mg three times daily. He presents to the clinic with concerns of reddish orange urine. He fears he has blood in his urine. Which most likely caused this condition?
    A. Carbidopa/levodopa.
    B. Entacapone.
    C. Amantadine.
    D. Hemorrhagic cystitis.

Patient Cases *(continued)*

19. L.L. is a 47-year-old man with Parkinson disease. He takes carbidopa/levodopa 50 mg/200 mg orally four times daily. His wife states that he cannot sit still during the day. He is constantly moving, and she fears his disease is worsening. Which is the best therapy for L.L.?
    A. Add ropinirole.
    B. Add selegiline.
    C. Increase the carbidopa/levodopa dose.
    D. Decrease the carbidopa/levodopa dose.

20. C.A. is a 70-year-old with tremors in his right hand that have progressively worsened for the past 6 months. He has difficulty walking. He also has backaches and no longer plays golf. In addition, he is losing his sense of taste. His wife notes that he is moving more slowly and that his handwriting has deteriorated. He is given a diagnosis of Parkinson disease. Which is the best treatment for this man?
    A. Trihexyphenidyl.
    B. Rasagiline.
    C. Carbidopa/levodopa.
    D. Ropinirole.

IV. HEADACHE

A. Definitions
    1. Migraine with aura: At least two attacks with at least three of the following: One or more fully reversible aura symptoms, at least one aura symptom for more than 4 minutes, or two or more symptoms occurring in succession; no single aura symptom lasts more than 60 minutes; headache follows aura within 60 minutes
    2. Migraine without aura: At least five attacks of headache lasting 4–72 hours with at least two of the following: Unilateral location, pulsating quality, intensity moderate or severe, aggravation by walking stairs or similar routine physical activity. During headache, at least one of the following: Nausea or vomiting, photophobia, phonophobia
    3. Tension: At least 10 previous headaches, each lasting from 30 minutes to 7 days, with at least two of the following: Pressing or tightening (nonpulsating) quality, intensity mild to moderate, bilateral location, no aggravation with physical activity
    4. Cluster: Several episodes, short-lived but severe, of unilateral, orbital, supraorbital, or temporal pain. At least one of the following must occur: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, facial sweating, miosis, ptosis, or eyelid edema.
    5. Analgesic rebound headache: If patients use analgesics often (usually defined as more than three times weekly), they may develop analgesic rebound headache. Patients with this condition usually present with a chronic daily headache, for which they take simple or narcotic analgesics. Treatment consists of the withdrawal of all analgesics (but not prophylactic medications).

B. Epidemiology
   1. Migraine: 15%–17% of women, 5% of men
   2. Tension: 88% of women, 69% of men
   3. Cluster: 0.01%–1.5% of population; ratio of men to women is 6:1

C. Treatment
   1. Migraine
      a. Prophylaxis should be considered if any of the following criteria are met: Migraines are recurrent and interfere with daily routine, migraines are frequent, patient has inefficacy or inability to use acute therapy, patient prefers prophylaxis as therapy, cost of acute medications is problematic, adverse effects with acute therapies occur, or migraine presentation is uncommon.
         i. General principles
            (a) Use lowest effective dose.
            (b) Give adequate trial (2–3 months).
            (c) If the patient has a coexisting condition, consider prophylaxis choice (e.g., β-blockers are contraindicated in patients with asthma but beneficial in patients with hypertension).
         ii. Medications with established efficacy
            (a) Erenumab-aooe
            (b) Fremanezumab-vfrm
            (c) Frovatriptan (for menstrually associated migraine, short-term prophylaxis only)
            (d) Galcanezumab-gnlm
            (e) Metoprolol
            (f) Onabotulinum toxin A
            (g) Petasites (butterbur extract)
            (h) Propranolol
            (i) Timolol
            (j) Topiramate
            (k) Valproate
         iii. Medications with probable efficacy
            (a) Amitriptyline
            (b) Atenolol
            (c) Fenoprofen
            (d) Histamine, subcutaneous
            (e) Ibuprofen
            (f) Ketoprofen
            (g) Magnesium (recommend magnesium citrate for better absorption)
            (h) MIG-99 (feverfew extract)
            (i) Nadolol
            (j) Naproxen/naproxen sodium
            (k) Naratriptan (for menstrually associated migraine, short-term prophylaxis only)
            (l) Riboflavin
            (m) Venlafaxine
            (n) Zolmitriptan (for menstrually associated migraine, short-term prophylaxis only)

iv. Medications with possible efficacy
    (a) Candesartan
    (b) Carbamazepine
    (c) Clonidine
    (d) Coenzyme Q_{10}
    (e) Cyproheptadine
    (f) Estrogen
    (g) Flurbiprofen
    (h) Guanfacine
    (i) Lisinopril
    (j) Mefenamic acid
    (k) Nebivolol
    (l) Pindolol
v. Medications with conflicting or inadequate evidence of efficacy: Acetazolamide, aspirin, bisoprolol, fluoxetine, fluvoxamine, gabapentin, hyperbaric oxygen, indomethacin, nicardipine, nifedipine, nimodipine, omega-3, protriptyline, verapamil
vi. Medications that are possibly ineffective, probably ineffective, or ineffective: Acebutolol, botulinum toxin, clomipramine, clonazepam, lamotrigine, montelukast, nabumetone, oxcarbazepine, telmisartan
vii. Calcitonin gene-related peptide antagonists are highly effective in refractory migraine headache prophylaxis
    (a) Erenumab-aooe (Aimovig): Dose: 70–140 mg subcutaneously monthly
    (b) Fremanezumab-vfrm (Ajovy): Dose: 225 mg subcutaneously monthly or 675 mg subcutaneously quarterly (administered as three separate injections)
    (c) Galcanezumab-gnlm (Emgality): Dose: Two consecutive doses of 120 mg subcutaneously for a total of a 240-mg loading dose, followed by doses of 120 mg subcutaneously monthly
    (d) Adverse effects: Injection site reactions; severe constipation (Aimovig only)

b. Acute treatment
    i. Triptans (Table 8)
        (a) Sumatriptan and zolmitriptan have nonoral administration routes (subcutaneous [sumatriptan], intranasal [sumatriptan and zolmitriptan], transdermal [sumatriptan]) that should be considered for patients with nausea or vomiting.
        (b) Orally disintegrating tablets are available for zolmitriptan and rizatriptan if patients do not have access to water; however, they do not work faster than oral tablets and are not absorbed sublingually.
        (c) All are contraindicated in patients with or at risk of coronary artery disease, stroke, uncontrolled hypertension, peripheral vascular disease, ischemic bowel disease, and pregnancy; they should not be used in patients with hemiplegic or basilar migraines.
        (d) Drug interactions: Contraindicated within 2 weeks of MAO inhibitors; do not use within 24 hours of ergotamines; caution with other serotonin-active medications. Propranolol increases serum concentrations of rizatriptan; thus, a 5-mg dose should be used with propranolol, and the dose should not exceed 15 mg/day.
    ii. Ergots
        (a) Dihydroergotamine has nonoral administration routes (subcutaneous, intravenous, and intranasal) that should be considered for patients with nausea or vomiting.
        (b) All are contraindicated in patients with, or at risk of, coronary artery disease, stroke, uncontrolled hypertension, peripheral vascular disease, ischemic bowel disease, and pregnancy; they should not be used in patients with hemiplegic or basilar migraines.

iii. Lasmiditan (Reyvow)
  (a) Mechanism of action: serotonin 1F receptor agonist
  (b) Dose: 50-200 mg at start of headache, may only take 1 dose per 24 hours
  (c) Adverse Effects: dizziness, fatigue, paresthesia, sedation
  (d) Avoid driving for at least 8 hours after dose.
iv. Ubrogepant (Ubrelvy)
  (a) Mechanism of Action: calcitonin gene-related peptide receptor antagonist
  (b) Dose 50-100 mg at start of headache, may repeat once after 2 hours
  (c) Adverse Effects: nausea, somnolence
  (d) Drug Interactions: avoid use with strong CYP3A4 inducers. Dose adjustments may be needed with moderate or weak CYP3A4 inhibitors or inducers and/or P-gp inhibitors
v. Rimegepant (Nurtec)
  (a) Mechanism of action: Calcitonin gene–related peptide receptor antagonist
  (b) Dose: 75 mg at start of headache; should not exceed 15 doses in 30 days
  (c) Adverse effects: Nausea
  (d) Drug interactions: Avoid use with strong CYP3A4 inhibitors, strong or moderate inducers, or P-gp and BCRP inhibitors; with moderate CYP3A4 inhibitors, avoid a second dose within 72 hours
vi. Nonsteroidal anti-inflammatory drugs (NSAIDs): Usually effective for only mild to moderate headache pain
vii. Opioids: Butorphanol has a nonoral administration route (intranasal) that should be considered for patients with nausea or vomiting.
viii. Isometheptene combination products: Conflicting evidence about efficacy
ix. Antiemetics: Prochlorperazine, metoclopramide, and chlorpromazine are most commonly used; there is suggestion that they have independent antimigraine action; all are available in nonoral forms. Often used in combination with acute migraine treatments to reduce nausea and vomiting
x. Status migrainosus: Attack of migraine, with headache phase lasting more than 72 hours despite treatment. Headache-free intervals of less than 4 hours (sleep not included) may occur.
  (a) Corticosteroids: Either intravenous or oral dosing
  (b) Dihydroergotamine: Intravenous dosing
  (c) Sodium valproate: Intravenous loading

2. Tension
  a. Prophylaxis
    i. Tricyclic antidepressants
    ii. Botulinum toxin
  b. Acute treatment
    i. Acetaminophen
    ii. NSAIDs
3. Cluster
  a. Prophylaxis
    i. Verapamil
    ii. Melatonin
    iii. Suboccipital injection of betamethasone
    iv. Lithium: May be efficacious at serum concentrations as low as 0.3 mmol/L
    v. Warfarin
    vi. Galcanezumab-gnlm (Emgality): Two consecutive doses of 120 mg subcutaneously for a total of a 240-mg loading dose, followed by doses of 120 mg subcutaneously monthly

b. Treatment
   i. Triptans: Subcutaneous and intranasal sumatriptan and intranasal zolmitriptan are effective. Oral formulations usually do not act quickly enough, but oral zolmitriptan showed efficacy in one trial.
   ii. Oxygen: 100% oxygen at 6–12 L/minute relieves pain in 50%–85% of patients.
   iii. Intranasal lidocaine: 20–60 mg as a nasal drop or spray (must be compounded)
   iv. Octreotide and 10% cocaine have been used with some effect.

Table 8. Selected Agents for Acute Treatment of Migraine Headache

	Dosage Forms	Tmax	Half-Life (hr)	Dose	Maximal Dose/24 Hr (mg)
Triptans					
Almotriptan (Axert)	Tablets 6.25 mg, 12.5 mg	1–3 hr	2–4	1 tablet, may repeat in 2 hr	25
Eletriptan (Relpax)	Tablets 20 mg, 40 mg	1 hr	4–5	1 tablet, may repeat in 2 hr	80
Frovatriptan (Frova)	Tablets 2.5 mg	2–4 hr	26	1 tablet, may repeat in 2 hr	7.5
Naratriptan (Amerge)	Tablets 1 mg, 2.5 mg	2–3 hr	6	1 tablet, may repeat in 4 hr	5
Rizatriptan (Maxalt)	Tablets 5 mg, 10 mg	1–1.5 hr	1.8	1 tablet, may repeat in 2 hr	30
	Orally disintegrating tablets 5 mg, 10 mg	1.6–2.5 hr	1.8	1 tablet, may repeat in 2 hr	30
Sumatriptan (Alsuma, Imitrex, Sumavel, Zecuity)	SC injection 4 mg, 6 mg	12 min	1.9	1 injection, may repeat in 1 hr	12
	Intranasal 5 mg, 20 mg	30 min	2	1 spray in one nostril, may repeat in 2 hr	40
	Tablets 25 mg, 50 mg, 100 mg	2 hr	2.5	1 tablet, may repeat in 2 hr	200
	Iontophoretic transdermal system 6.5 mg/4 hr	1.1 hr	3.1	1 patch, may repeat in 2 hr	13
Zolmitriptan (Zomig)	Tablets 2.5 mg, 5 mg	1.5 hr	3.75	1 tablet, may repeat in 2 hr	10
	Orally disintegrating tablets 2.5 mg, 5 mg	3 hr	3.75	1 tablet, may repeat in 2 hr	10
	Intranasal 2.5 mg, 5 mg	3 hr	3	1 spray in one nostril, may repeat in 2 hr	10

IM = intramuscular(ly); IV = intravenous(ly); SC = subcutaneous(ly).

Table 8. Selected Agents for Migraine Headache *(continued)*

	Dosage Forms	Tmax	Half-Life (hr)	Dose	Maximal Dose/24 Hr (mg)
Triptan/NSAID combination					
Sumatriptan/naproxen sodium (Treximet)	Tablets 85 mg/500 mg	1 hr/5 hr	2/19	1 tablet, may repeat in 2 hr	170/1000
Ergots					
Ergotamine tartrate (Ergomar)	Sublingual tablets 2 mg	Unknown	2	1 tablet under tongue, may repeat in 1 hr	6
Dihydroergotamine (DHE 45; Migranal)	Intranasal 4-mg ampules	0.9 hr	10	1 spray (0.5 mg) in each nostril, repeat in 15 min	3
	IV/IM/SC 1 mg/mL 1-mL vials	SC 15–45 min	9	1 mL IV/IM/SC, may repeat in 1 hr	2 mg IV; 3 mg IM/SC

IM = intramuscular(ly); IV = intravenous(ly); SC = subcutaneous(ly).

Patient Cases

21. M.R., a 34-year-old woman, has throbbing right-sided headaches. She has nausea, phonophobia, and photophobia with these headaches but no aura. She usually has headaches twice a month. She has hypertension and morbid obesity. She takes hydrochlorothiazide 25 mg/day orally for hypertension. Which drug is best for prophylaxis of her headaches?
    A. Propranolol.
    B. Indomethacin.
    C. Topiramate.
    D. Sumatriptan.

22. S.R. is a 54-year-old businessman with squeezing, band-like headaches that occur three or four times weekly. He rates the pain of these headaches as 7/10 and finds acetaminophen, aspirin, ibuprofen, naproxen, ketoprofen, and piroxicam only partly effective. He wants to take a prophylactic drug to prevent these tension headaches. Which drug is best for prophylaxis of his headaches?
    A. Propranolol.
    B. Topiramate.
    C. Amitriptyline.
    D. Rizatriptan.

23. D.S. is a 49-year-old male computer programmer who describes lancinating right-eye pain and tearing several times a day for 2–3 days in a row. He will have no episodes for 2–3 weeks but then will have recurrent episodes. In the office, he receives oxygen by nasal cannula during an episode, and his pain is relieved. He has a diagnosis of cluster headaches. Which drug is best for prophylaxis of his headaches?
    A. Atenolol.
    B. Valproate.
    C. Nortriptyline.
    D. Lithium.

Patient Cases *(continued)*

24. M.K. is a 44-year-old woman with right-sided headaches of moderate intensity that are accompanied by severe nausea and vomiting. Which drug is best for M.K.'s migraine headaches?
    A. Almotriptan.
    B. Naratriptan.
    C. Promethazine.
    D. Sumatriptan.

25. T.C. is a 30-year-old woman with migraine headaches. She takes sumatriptan 100 mg, which provides immediate relief. However, about 2 hours later, her headache symptoms return. Which would be best for her?
    A. Eletriptan 20 mg.
    B. Frovatriptan 2.5 mg.
    C. Naproxen 250 mg.
    D. Topiramate 25 mg.

V. MULTIPLE SCLEROSIS

A. Definitions
    1. Autoimmune disorder with areas of CNS demyelination and axonal transaction
    2. Clinical course
        a. Clinically isolated syndrome; first clinical presentation for which the 2017 diagnostic criteria for MS have not been met
        b. Classified as relapsing-remitting, secondary progressive, and primary progressive with subclassification according to disease activity and progression: Relapsing-remitting: 85% of patients at diagnosis, develops into progressive disease in 50% of patients within 10 years

B. Epidemiology
    1. Diagnosis is usually at 20–50 years of age.
    2. Twice as many women as men develop MS.
    3. Whites and people of northern European heritage are more likely to develop MS.
    4. Risk factors: Family history of MS, autoimmune disease, or migraine; personal history of autoimmune disease or migraine; cigarette smoke exposure, obesity (especially in childhood and adolescence), vitamin D deficiency, geography, genetic factors, Epstein-Barr virus

C. Treatment
    1. Acute relapses are treated with high-dose corticosteroids.
        a. Intravenous methylprednisolone: Usual dose is 1 g/day as one dose or as divided doses for 3–5 days.
        b. Oral prednisone: Usual dose is 1250 mg/day given every other day for five doses.
        c. Intravenous adrenocorticotropic hormone
        d. Neurologic recovery is the same with or without an oral prednisone taper.

2. Disease-modifying therapies (Table 9)
    a. Alemtuzumab (Lemtrada)
        i. Mechanism of action: Binds to CD52, a cell surface antigen on T cells, B cells, natural killer cells, monocytes, and macrophages; causes lysis of T and B cells
        ii. Adverse effects
            (a) Autoimmunity including thyroid disorders (34%), immune thrombocytopenia, glomerular nephropathies
            (b) Infusion reactions (e.g., anaphylaxis, angioedema, bronchospasms, nausea, urticaria) occur in up to 92% of patients and necessitate corticosteroids during treatment.
            (c) Increased infections: Screen for herpes zoster and immunize, if needed; screen for tuberculosis before initiating therapy; prophylaxis for herpes infections is necessary during treatment.
            (d) May increase risk of thyroid cancer, melanoma, and lymphoma
            (e) Administered only under a restricted distribution program
        iii. Avoid live virus vaccines during treatment; complete all vaccines 6 weeks before initiating therapy.
    b. β-Interferons (Avonex, Betaseron, Extavia, Plegridy, Rebif)
        i. Mechanism of action: Suppress T-cell activity, down-regulate antigen presentation by major histocompatibility complex class II molecules, decrease adhesion molecules and matrix metalloproteinase 9, increase anti-inflammatory cytokines, and decrease inflammatory cytokines
        ii. Adding polyethylene glycol to interferon-β1a decreases the frequency of injections.
        iii. Injection site reactions: More common in subcutaneously administered products. May help to bring a drug to room temperature before injection, ice the injection site, and rotate injection sites
        iv. Flu-like symptoms: Usually dissipate in 2–3 months. May help to inject the dose in the evening. Begin at the 0.25- to 0.5-mg dose and slowly increase, and use ibuprofen or acetaminophen.
        v. Neutralizing antibodies: Develop in some patients 6–18 months after treatment begins; frequency and administration route affect neutralizing antibody development; relapse rates are higher in patients with persistently high antibody titers; antibodies may disappear even during continued treatment; show cross-reactivity with other β-interferons
        vi. Avoid in severe, untreated depression.
    c. Dimethyl fumarate (Tecfidera)
        i. Mechanism of action: Antioxidant and cytoprotective; inhibits proinflammatory cytokines, increases anti-inflammatory cytokines
        ii. Adverse effects
            (a) Skin flushing: Occurs in up to 38% of patients, usually within 30–45 minutes of dosing; involves the face, chest, and neck; dissipates after 15–30 minutes; peaks within first month of therapy and decreases thereafter; aspirin may block flushing, taking with food helps prevent
            (b) GI events: Occur in up to 41% of patients; peak within first month of therapy and decrease thereafter
            (c) Lymphocytes decrease by 30% in the first year of therapy and then stabilize.
        iii. Indicated for use in pregnancy

d. Glatiramer acetate (Copaxone)
    i. Mechanism of action: Decreases type 1 helper T cells; increases type 2 helper T cells; increases production of nerve growth factors
    ii. Injection site reactions: Icing the site before and after injection and rotating the injection site may help.
    iii. Systemic reactions: May involve flushing, chest tightness, palpitations, anxiety, and shortness of breath; this is noncardiac; recurrence is infrequent
    iv. Avoid use in pregnancy unless clearly needed.
e. Fingolimod (Gilenya)
    i. Mechanism of action: Binds to the S1P receptor 1, 3, 4, 5 expressed on T cells, prevents activation of T cells
    ii. Indicated for patients 10 years and older
    iii. Contraindicated in patients with myocardial infarctions, unstable angina, stroke, TIAs, or decompensated heart failure necessitating hospitalization or class III/IV heart failure, history of Mobitz type II second- or third-degree atrioventricular block or sick sinus syndrome unless patient has a pacemaker, baseline QTc interval greater than or equal to 500 milliseconds, or treatment with class Ia or class III antiarrhythmic drugs
    iv. Patients must be monitored for bradycardia for 6 hours after the first dose; if therapy is discontinued for more than 2 weeks, patients must be re-monitored.
    v. Adverse effects
        (a) Bradycardia: ECG is recommended within 6 months for patients using antiarrhythmics (including β-blockers and calcium channel blockers), those with cardiac risk factors, and those with slow or irregular heartbeat. Heart rate returns to baseline within 1 month of continued dosing.
        (b) Atrioventricular conduction delays: First- and second-degree block
        (c) Decrease in lymphocytes: A recent CBC should be available before therapy begins. Infections may be more common. Discontinue therapy for serious infections; test patients without varicella zoster vaccine or infection history for varicella zoster virus antibodies, and immunize antibody-negative patients (wait 1 month to initiate fingolimod).
        (d) Macular edema: Ophthalmologic evaluation at baseline and 3–4 months after fingolimod initiation; a history of uveitis or diabetes mellitus increases risk
        (e) Respiratory effects: Decreases in forced expiratory volume over 1 second and diffusion lung capacity for carbon monoxide can occur.
        (f) Elevation of liver enzymes
        (g) Hypertension: Monitor during treatment.
        (h) Extended effects of drug for up to 2 months after discontinuation necessitate extended monitoring for many adverse effects.
    vi. Drug interactions
        (a) Ketoconazole: Increased fingolimod
        (b) Vaccines: Less effective during and 2 months after fingolimod treatment; avoid live, attenuated vaccines
    vii. Avoid pregnancy during treatment and for 2 months after treatment.
    viii. Medication guide required

f. Mitoxantrone (Novantrone)
   i. Mechanism of action: Decreases monocytes and macrophages, inhibits T and B cells
   ii. Indicated for secondary progressive, progressive-relapsing, and worsening-relapsing-remitting MS; used infrequently because of toxicity
   iii. Because of the potential for toxicity, mitoxantrone is reserved for patients with rapidly advancing disease whose other therapies have failed.
   iv. Patients taking mitoxantrone should not receive live virus vaccines; other vaccines should be held for 4–6 weeks after dose.
   v. Cardiotoxicity: Echocardiograms or multi-gated acquisition scans must be done at baseline and before each infusion. Systolic dysfunction occurs in about 12% of patients; congestive heart failure occurs in about 0.4%. Cardiotoxicity is not dose-, sex-, or age-related. Cyclooxygenase 2 inhibitors should be avoided; cumulative lifetime maximum dose of 140 mg/m^2
   vi. Therapy-related acute leukemia occurs in about 0.8% of patients.
   vii. Other laboratory tests (CBC, bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, and pregnancy test) must be done before each infusion.
   viii. Avoid pregnancy during treatment.
g. Natalizumab (Tysabri)
   i. Mechanism of action: Blocks T-cell entry into the CNS
   ii. Indicated for relapsing forms of MS but distributed through restricted distribution program because of progressive multifocal leukoencephalopathy risk (0.24%)
   iii. Adverse effects
      (a) Hypersensitivity reactions: Itching, dizziness, fever, rash, hypotension, dyspnea, chest pain, anaphylaxis, usually within 2 hours of administration
      (b) Progressive multifocal leukoencephalopathy: Rapidly progressive viral CNS infection; usually results in death or permanent disability. Patient selection guidelines are for patients with relapsing-remitting disease whose other treatment (efficacy or intolerability) has failed or who have an aggressive initial course; should not be used in combination with other disease-modifying therapies. On January 20, 2012, an FDA-issued drug safety communication associated positive tests for John Cunningham virus (JCV) antibodies as a risk factor for progressive multifocal leukoencephalopathy. Thus, patients with all three of the following risk factors – presence of anti-JCV antibodies, longer natalizumab treatment duration (especially beyond 2 years), and previous treatment with an immunosuppressant medication (mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil) – have a 1.1% chance of developing progressive multifocal leukoencephalopathy.
      (c) Antibodies to natalizumab, associated with increased relapses and hypersensitivity reactions, develop in 9%–12% of patients.
      (d) Severe liver toxicity, depression
h. Ocrelizumab (Ocrevus)
   i. Mechanism of action: Thought to bind to CD20 on pre-B and mature B cells
   ii. Indicated for relapsing or primary progressive forms of MS
   iii. Pharmacokinetics: 2-compartment model with central compartment volume 2.78 L. Terminal half-life 26 days
   iv. Adverse effects
      (a) Infectious: Respiratory infections, herpes virus infections
      (b) Psychiatric: Depression
      (c) Infusion reactions
      (d) GI: Diarrhea
      (e) Malignancies

v. Must test for hepatitis B before first dose, contraindicated if positive
vi. Premedicate with methylprednisolone and an antihistamine before each infusion.
vii. Administer necessary vaccines 4 weeks before dose (live, live-attenuated) or 2 weeks before dose (non-live).

i. Ozanimod (Zeposia)
i. Mechanism of action: Sphingosine-1-phosphate receptor modulator
ii. Indicated for relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting, and active secondary progressive disease
iii. Dose: Titrate dose to maintenance dose of 0.92 mg orally daily.
iv. Contraindications: Within the past 6 months, patient has experienced a myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure with hospitalization, class III or IV heart failure, Mobitz type II second-degree heart block, third-degree atrioventricular block, sick sinus syndrome, sinoatrial block, unless a functioning pacemaker
v. Adverse effects: Increased risk of infection, bradyarrhythmia and atrioventricular conduction delays, hepatotoxicity, teratogenicity, hypertension, decreased pulmonary function, macular edema, orthostatic hypotension
vi. Drug interactions: Avoid CYP2C8 inducers and inhibitors, BCRP inhibitors, and live-attenuated vaccinations.

j. Teriflunomide (Aubagio)
i. Mechanism of action: Prevents activation of lymphocytes
ii. Indicated for relapsing forms of MS
iii. Pharmacokinetics: Long half-life (8–19 days); takes about 3 months to reach steady-state concentrations; takes an average of 8 months to eliminate drug (serum concentrations less than 0.02 mcg/mL) and may take up to 2 years
iv. Adverse effects
(a) Hepatotoxicity may occur; teriflunomide should not be used in patients with preexisting liver disease or with ALT more than 2 times the upper limit of normal. Discontinue if severe liver damage occurs.
(b) GI effects: Diarrhea, nausea
(c) Dermatologic effects: Alopecia, rash (Stevens-Johnson syndrome)
(d) Infection: Neutropenia and lymphopenia may occur; tuberculosis infections reported (negative tuberculosis skin test required at baseline); live virus vaccinations should not be administered
(e) Teratogenic: Contraindicated in women of reproductive potential; negative pregnancy test at baseline; adequate contraception should be ensured; if pregnancy desired for men or women, teriflunomide should be discontinued, accelerated elimination procedures should be undertaken, and two serum concentrations less than 0.02 mcg/mL taken 14 days apart should be confirmed
v. Accelerated elimination procedures
(a) Cholestyramine 8 g every 8 hours for 11 days (if not tolerated, may use 4 g)
(b) Activated charcoal powder 50 g every 12 hours for 11 days

k. Siponimod (Mayzent)
i. Mechanism of action: Sphingosine-1-phosphate receptor modulator, blocking the ability of lymphocytes to leave lymph nodes and enter systemic circulation
ii. Indication: Relapsing forms of MS, including relapsing-remitting and active secondary progressive disease
iii. Adverse effects
(a) Common: Headache, hypertension, increased liver function tests

(b) Serious: Infections, macular edema, bradyarrhythmia, atrioventricular conduction delays, decreased pulmonary function, hepatotoxicity

iv. Contraindications:
(a) *CYP*3*3* genotype
(b) Myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure, class III/IV heart failure in the past 6 months
(c) Mobitz type II second-degree, third-degree atrioventricular block, sick sinus syndrome

v. Drug interactions
(a) Avoid live-attenuated vaccines. during and up to 4 weeks after treatment.
(b) CYP 2C9, 3A4 moderate or strong inhibitors and inducers should be avoided.

l. Cladribine (Mavenclad)
i. Mechanism of action: Not established for MS, but may be the result of cytotoxic effects on B and T lymphocytes
ii. Indication: Relapsing forms of MS, including relapsing-remitting and active secondary progressive disease
iii. Adverse effects
(a) Common: Upper respiratory tract infection, headache, lymphopenia
(b) Serious: Hepatotoxicity, infection, graft-vs.-host disease after transfusion
iv. Contraindications: Current malignancy, women of reproductive potential, HIV infection, active chronic infections (e.g., hepatitis, tuberculosis), breastfeeding
v. Drug interactions: Avoid immunosuppressive and antiviral/antiretroviral drugs, avoid live-attenuated vaccinations, hematotoxic drugs

3. Symptomatic therapies
a. Patients may have fatigue, spasticity, urinary incontinence, pain, depression, cognitive impairment, fecal incontinence, constipation, pseudobulbar affect, and sexual dysfunction; standard therapies should be used for these symptoms.
b. Fatigue: Treatment may be nonpharmacologic (rest, assistive devices, cooling strategies, exercise, stress management) or pharmacologic (amantadine, methylphenidate).
c. Spasticity: Therapies must be centrally acting.
i. First line: Baclofen, tizanidine
ii. Second line: Dantrolene, diazepam
iii. Third line: Intrathecal baclofen
iv. Focal spasticity: Botulinum toxin
d. Walking impairment: Dalfampridine (Ampyra)
i. Indicated to improve walking in patients with MS by improving walking speed
ii. Potassium channel blocker, prolongs action potentials in demyelinated neurons
iii. Dose: 10 mg orally twice daily; extended-release tablets
iv. Contraindicated in patients with a history of seizures or moderate or severe renal impairment
v. Adverse effects: Seizures, urinary tract infections, insomnia
e. Pseudobulbar affect: Dextromethorphan/quinidine
i. Affects 10% of patients
ii. Episodes of inappropriate laughing or crying
iii. Dextromethorphan prevents excitatory neurotransmitter release.
iv. Low-dose quinidine blocks first-pass metabolism of dextromethorphan, thus increasing dextromethorphan serum concentrations.

Table 9. Comparison of Disease-Modifying Therapies

Drug (Brand)	Dose	Route	Frequency	Adverse Effects
Alemtuzumab (Lemtrada)	First course: 12 mg/day over 4 hr × 5 days Second course: 12 mg/day over 4 hr × 3 days 12 mo after first course	IV	Daily for 5 days; then daily for 3 days 12 mo later	Infusion reaction 92% Rash 53% Thyroid disorders 34% Headache 52% Infections 13%–19%
Cladribine (Mavenclad)	Recommended cumulative dose 3.5 mg/kg orally divided into 2 yearly courses. See labeling for detail administration schedule.	PO	2 cycles annually	Upper respiratory tract infection (38%) Headache (25%) Lymphopenia (24%)
Dimethyl fumarate (Tecfidera)	120 mg twice daily × 7 days; then 240 mg twice daily	PO	Twice daily	Skin flushing 38% GI events 41%
Fingolimod (Gilenya)	0.5 mcg	PO	Daily	Increased AST/ALT 14% Infections 13% Diarrhea 12% Hypertension 6% Bradycardia 4% Blurred vision 4% Lymphopenia 4% Leukopenia 3%
Glatiramer acetate (Copaxone)	20 mg 40 mg	SC SC	Daily Three times/wk	Injection site reaction 90% Systemic reaction 15%
Interferon-β-1a (Avonex)	30 mcg	IM	Weekly	Flu-like symptoms 61% Anemia 8% Depression
Interferon-β-1a (Rebif)	22 mg or 44 mcg	SC	Three times/wk	Flu-like symptoms 28% Injection site reactions 66% Leukopenia 22% Increased AST/ALT 17%–27% Depression
Interferon-β-1b (Betaseron)	0.25 mg	SC	Every other day	Flu-like symptoms 60%–76% Injection site reactions 50%–85% Asthenia 49% Menstrual disorder 17% Leukopenia 10%–16% Increased AST/ALT 4%–19%
Mitoxantrone (Novantrone)	12 mg/m^2 Up to 140 mg/m^2 (lifetime dose)	IV	Every 3 mo	Nausea 76% Alopecia 61% Menstrual disorders 61% Urinary tract infection 32% Amenorrhea 25% Leukopenia 19% γ-Glutamyl transpeptidase increase of 15%

Table 9. Comparison of Disease-Modifying Therapies *(continued)*

Drug (Brand)	Dose	Route	Frequency	Adverse Effects
Natalizumab (Tysabri)	300 mg	IV	Every 4 wk	Headache 38% Fatigue 27% Arthralgia 19% Urinary tract infection 20% Hypersensitivity reaction < 1% Progressive multifocal leukoencephalopathy (PML)
Ocrelizumab (Ocrevus)	300 mg, followed by 300 mg 2 wk later; then 600 mg	IV	Every 6 mo after initial doses	Injection site reactions 34% Risk of infection
Pegylated interferon-β--1a (Plegridy)	125 mcg	SC	Every 2 wk	Injection site reactions 62% Flu-like symptoms 47% Headache 44% Myalgia 19%
Siponimod (Mayzent)	Depending on CYP2C9 genotype, usual dose titrate over 5 days to 1 mg	PO	Daily	Headache 15% Hypertension 13% Increased liver function tests 11% Falls 11% Peripheral edema 8% Nausea 7% Dizziness 7% Diarrhea 7% Bradycardia 6% Pain 6%
Teriflunomide (Aubagio)	7 mg or 14 mg	PO	Daily	Diarrhea 15%–18% Nausea 9%–14% Alopecia 10%–13% Neutropenia 10%–15% Lymphopenia 7%–10% Elevated ALT 3%–5% Hypertension 4% Peripheral neuropathy 1%–2% Reactivation of tuberculosis

Patient Cases

Questions 26–28 pertain to the following case:

S.F. is a 36-year-old woman with a history of MS. This morning, her left arm became progressively weaker over about 3 hours. She was previously healthy except for a broken radius when she was 13 years old and a case of optic neuritis when she was 25 years old.

26. Which treatment is best for treating S.F.'s exacerbation?
    A. Interferon beta-1a.
    B. Glatiramer acetate.
    C. Methylprednisolone.
    D. Fingolimod.

27. Which therapy is best for S.F. to prevent further exacerbations?
    A. Methylprednisolone.
    B. Baclofen.
    C. Glatiramer acetate.
    D. No treatment.

28. S.F. elects to start fingolimod. Which would be best to monitor every 6 months while she is taking fingolimod?
    A. ECG
    B. Sodium
    C. Pulmonary function tests
    D. Renal function tests

29. B.B. is a 33-year-old woman with a recent diagnosis of multiple sclerosis. Her neurologist wants you to discuss with her the potential medications to prevent exacerbations. During the discussion, you find that she and her husband are planning to have a child in the next few years and that she is terrified of needles. Which is best for B.B.?
    A. Glatiramer acetate.
    B. Mitoxantrone.
    C. Teriflunomide.
    D. Dimethyl fumarate.

VI. PERIPHERAL NEUROPATHY

A. Broad range of diseases that damage nerves outside the brain and spinal cord. Other terms for peripheral neuropathy include *peripheral neuritis*, *polyneuropathy*, and *polyneuritis*.
    1. More than 100 types; each is unique
    2. Can be classified as acute or chronic; also, can be predominantly motor, mixed motor and sensory, or predominantly sensory

B. Epidemiology
   1. 30 million people in the United States have some form of peripheral neuropathy.
   2. The most common form is diabetic neuropathy. Diabetic peripheral neuropathy can occur before an official diagnosis of diabetes and may be the presenting symptom of diabetes.

C. Clinical Course
   1. Patients may initially present with altered sensation, pain, weakness, or autonomic symptoms. Symptoms typically are present distally in the initial stages.
   2. Symptoms may be bilateral or unilateral, symmetrical, or asymmetrical.
   3. Symptoms progress proximally. In advanced stages, distal wasting, weakness, absent deep tendon reflexes, and glove and stocking sensory loss can occur.

D. Diagnosis
   1. Complete medical history, medication history, and neurologic examination
   2. Electromyelogram and nerve conduction studies
   3. Laboratory tests to include serum chemistry, CBC, toxicology screen, vitamin B_{12} concentration, immune panel

E. Causes

Table 10. Common Causes of Acute Severe Peripheral Neuropathy

Cause	Predominantly Motor	Mixed	Predominantly Sensory
Guillain-Barré syndrome	+	+	—
Vasculitis	—	+	—
Diabetes mellitus	—	+	+
Drugs[a]	—	+	+
Porphyria	+	—	—
Diphtheria	—	+	—
Paraneoplastic neuropathy	—	+	+
Acute idiopathic sensory neuropathy	—	—	+
Critical illness	+.	+	—
Chronic inflammatory demyelinating polyneuropathy	—	+	—

[a]Examples include nitrofurantoin, vincristine, cisplatin, and reverse transcriptase inhibitors.

F. Treatments
   1. Most treatments are directed toward symptomatic relief of the sensory component of neuropathies.
   2. Systemic and topical treatments may be combined.
   3. If an immune component is involved, treatment options include immune modulation. Recommendations for specific regimens vary with the disease diagnosis.
      a. Prednisone
      b. Immunoglobulin
      c. Plasmapheresis
      d. Immunosuppressants (e.g., cyclosporine, azathioprine, tacrolimus, sirolimus)

Table 11. Pharmacotherapy for Neuropathic Pain

ORAL			
Therapy	**Route**	**Starting Dose**	**Maintenance Dose**
First Line			
Tricyclic antidepressants	PO	10–25 mg at bedtime	Increase by 10- to 25-mg increments to 100–150 mg at bedtime
Gabapentin	PO	300 mg three times daily	Increase by 300- to 400-mg increments to 2400–6000 mg/day in three or four doses
Second Line			
Carbamazepine	PO	200 mg twice daily	Increase by 200-mg increments to 200–400 mg three or four times daily; follow serum concentrations on doses greater than 600 mg/day
Tramadol	PO	50 mg two or three times daily	Increase by 50-mg increments to a maximum of 100 mg four times daily
Duloxetine	PO	30 mg daily	Increase by 30- to 60-mg increments up to 120 mg daily
Pregabalin	PO	50 mg three times daily	Increase by 300 mg/day
Third Line			
Oxcarbazepine	PO	150–300 mg twice daily	Increase by 300-mg increments to 600–1200 mg twice daily
Lamotrigine	PO	25 mg once daily	Increase by 25-mg increments weekly to 100–200 mg twice daily
Topiramate	PO	25–50 mg at bedtime	Increase by 50-mg increments weekly to 200 mg twice daily
Venlafaxine	PO	37.5–75 mg once daily	Increase by 75-mg increments to 150–225 mg/day
Valproate	PO	250 mg two or three times daily	Increase by 250-mg increments up to 1500 mg/day
Fourth Line			
Bupropion SR	PO	150 mg daily	After 1 wk, increase to 150 mg twice daily
Tiagabine	PO	4 mg daily	Increase to 4–12 mg twice daily
Levetiracetam	PO	250 mg at bedtime	Increase by 250- to 500-mg increments to 1500 mg twice daily
Zonisamide	PO	100 mg at bedtime	Increase by 100-mg increments to 400–600 mg at bedtime
Mexiletine	PO	200 mg daily	Increase by 200-mg increments to a maximum of 200 mg three times daily
Phenytoin	PO	200 mg at bedtime	Increase by 100 mg increments to 300–400 mg daily, follow serum concentrations
Newer Drugs			
Milnacipran	PO	12.5 mg at bedtime for 1 day	12.5 mg twice daily for 2 days; then 25 mg twice daily for 4 days; then 50 mg twice daily. May increase up to 100 mg twice daily
Lacosamide	PO	50 mg twice daily	Increase to 100 mg twice daily after 1 wk. May increase up to 200 mg twice daily

Table 11. Pharmacotherapy for Neuropathic Pain *(continued)*

TOPICAL AGENTS			
Therapy	**Route**	**Starting Dose**	**Maintenance Dose**
Over the Counter			
Capsaicin 0.075%	Topical	Apply to affected region three or four times daily	Continue starting dose
Salicylate 10%–25%	Topical	Apply to affected region three or four times daily	Continue starting dose
Menthol 16%/ camphor 3%	Topical	Apply to affected region three or four times daily	Continue with starting dose
Prescription			
Lidocaine 2.5%/ prilocaine 2.5%	Topical	Apply to affected region three or four times daily	Continue with starting dose
Lidocaine patch 5%	Topical	Apply over adjacent intact skin	Increase up to 3 patches worn for up to 12 hr daily
Doxepin 5%	Topical	Apply to affected region twice daily	Continue with starting dose
Diclofenac sodium gel 1%	Topical	Apply to affected region three or four times daily	Continue with starting dose
Compounded Prescription Products			
Ketoprofen 5%/ amitriptyline 2%/ tetracaine 1%	Topical	Apply to affected area twice daily	Increase up to four times daily
Ketoprofen 10%/ cyclobenzaprine 1%/ lidocaine 5%	Topical	Apply to affected region twice daily	Increase up to four times daily
Ketamine 5%/ amitriptyline 4%/ gabapentin 4%	Topical	Apply to affected region twice daily	Increase up to thrice daily
Carbamazepine 5%/ lidocaine 5%	Topical	Apply to affected region twice daily	Increase up to four times daily
Amitriptyline 2%/ baclofen 2%	Topical	Apply to affected region three or four times daily	Continue with starting dose

Patient Case

Questions 30 and 31 pertain to the following case.

S.B. is 55-year-old man referred to a neurologist for numbness, burning, and tingling in his feet that has progressively worsened over the past year. On neurologic examination, he has decreased sensations bilaterally to mid-calf. He takes no medications except for nonprescription analgesics as needed for pain. His current body mass index (BMI) is 32 kg/m^2.

30. Which test would best determine the cause of S.B.'s neuropathy?

    A. Potassium.
    B. Hemoglobin A1C (A1C).
    C. Serum creatinine.
    D. White blood cell count.

31. Which therapy is best for S.B.?

    A. Naproxen.
    B. Tramadol.
    C. Nortriptyline.
    D. Prednisone.

32. A meta-analysis of treatments for neuropathic pain included data from 26 clinical trials (2007;9:36). The following results of the review included these data.

Treatment	No. Needed to Treat
Tricyclic antidepressants	2.1
SNRIs	5.1
SSRIs	7

Given these data, which would be most effective for neuropathic pain?

A. Duloxetine.
B. Sertraline.
C. Amitriptyline.
D. Venlafaxine.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: D
Juvenile myoclonic epilepsy is a type of generalized epilepsy that consists of myoclonic and tonic-clonic seizures. Phenytoin (Answer B) and oxcarbazepine (Answer C) can increase myoclonic seizures. Although valproate (Answer A) is effective for JME, it is associated with several teratogenic effects. Because this patient is a woman of childbearing potential, it is advisable to avoid valproate even though she takes oral contraceptives. Levetiracetam (Answer D) is effective for JME and has much less risk of teratogenic effects.

2. Answer: A
Interactions with oral contraceptives are a concern with several ASMs. In these cases, alternative forms of birth control (Answer B) may be necessary. Decreased effectiveness of oral contraceptives may be associated with breakthrough bleeding (Answer C). In addition, oral contraceptives can alter the effectiveness of ASMs (Answer D). However, no evidence supports that levetiracetam alters oral contraceptive effectiveness or that oral contraceptives change the effectiveness of levetiracetam, making Answer A correct.

3. Answer: A
Carbamazepine (Answer B) can increase seizures in JME. Cannabidiol (Answer C) has only been shown effective in Dravet syndrome and Lennox-Gastaut syndrome. Valproate (Answer D) should be avoided in this patient because of its teratogenic adverse effects. Lamotrigine (Answer A) is a reasonable alternative that is effective for JME and is not associated with an increased risk of teratogenic adverse effects.

4. Answer: B
Lorazepam (Answer B) is the drug of choice for status epilepticus. Lorazepam is less lipophilic than diazepam (Answer A); therefore, lorazepam does not redistribute from the CNS as quickly. Phenytoin (Answer C) and phenobarbital (Answer D) should be held in reserve for maintenance therapy or refractory status epilepticus.

5. Answer: D
Phenytoin has nonlinear pharmacokinetics. A small increase in dose may result in a large increase in serum concentration. Therefore, without doing any calculations, we can surmise that an increase from 300 mg/day to 600 mg/day would more than double the serum concentration (Answer D). Lower increases (Answers A–C) would be unlikely with an increase in dose this large.

6. Answer: D
Phenytoin (Answer A) and carbamazepine (Answer C) can increase absence seizure frequency. Valproate (Answer B) is an alternative, but it is less desirable because of its adverse effect profile. Ethosuximide (Answer D) is useful for absence seizures and had fewer adverse effects than valproate in a randomized study.

7. Answer: D
Although hepatotoxicity (Answer A) is a possible adverse effect of carbamazepine, it is most likely to occur within the first few months of starting carbamazepine. Acne (Answer B) and gingival hyperplasia (Answer C) are adverse effects associated with phenytoin. Diplopia (Answer D) is a common adverse effect associated with higher concentrations of carbamazepine.

8. Answer: C
Hepatoxicity (Answer A) is associated with several ASMs but not with levetiracetam. Alopecia (Answer D) is a common adverse effect of valproate. Depression (Answer C) and agitation are common adverse effects of levetiracetam. Zonisamide is associated with a 1% increase in the risk of renal stones (Answer B).

9. Answer: D
Carbamazepine forms an active epoxide intermediate (carbamazepine-10,11-epoxide), whereas oxcarbazepine does not (Answer D). Carbamazepine induces more liver enzymes than oxcarbazepine (Answer A). However, hyponatremia is more closely associated with oxcarbazepine than with carbamazepine (Answer C). Both drugs can cause allergic rashes (Answer B).

10. Answer: C
Immediate discontinuation of oxcarbazepine (Answer A) would likely increase seizures. Topiramate (Answer B) is associated with an increased risk of teratogenic adverse effects. Lamotrigine (Answer D) is considered safe during pregnancy, but changing medications increases the risk of seizures. In addition, lamotrigine pharmacokinetics change during

pregnancy, complicating its management. Continuing the patient's current medication (Answer C) is the best approach during pregnancy.

11. Answer: D
Nonmodifiable risk factors for stroke include age, race, and male sex. Somewhat modifiable risk factors include hypercholesterolemia and diabetes mellitus. Modifiable stroke risk factors include hypertension, smoking, and atrial fibrillation. Less well-documented risk factors include obesity, physical inactivity, alcohol abuse, hyperhomocystinemia, hypercoagulability, hormone replacement therapy, and oral contraceptives. Minimal cognitive impairment (Answer C) and osteoarthritis (Answers A and B) are not risk factors for stroke. Answer D is the only response that includes only risk factors for stroke.

12. Answer: C
There are many contraindications to administering tissue plasminogen activator for stroke, mainly focused on bleeding risk. There is no upper limit on age (Answer B). Breast cancer (Answer D) is not a contraindication for tissue plasminogen activator. Her symptoms began 6 hours ago, placing her outside the window for alteplase use (Answer C is correct; Answer A is incorrect).

13. Answer: C
Warfarin (Answer D) is only indicated for stroke prevention with atrial fibrillation. Other than modifying a partly modifiable risk factor for stroke, metformin (Answer A) has no benefit in preventing stroke. Celecoxib (Answer B) also has no benefit in preventing stroke and, according to some studies, may increase the risk of stroke. Aspirin and clopidogrel (Answer C) should be used together for 21 days after an acute stroke to reduce the risk of another stroke.

14. Answer: C
No therapy (Answer C) is an appropriate choice for this patient (CHA_2DS_2-VASc score of 0) because he is younger than 65 and has no other risk factors such as hypertension or a prosthetic valve. Apixaban (Answer A) would needlessly increase his risk of bleeding. A combination of aspirin and clopidogrel (Answer B) is not indicated to prevent a stroke in atrial fibrillation. The risk of stroke associated with atrial fibrillation can be reduced with the appropriate use of anticoagulants, making Answer D incorrect.

15. Answer: D
With a mitral valve replacement, the target INR is 2.5–3.5, making 3 (Answer D) an optimal target. An INR of 1.5 (Answer A) or 2 (Answer B) is too low for a valve replacement. An INR of 2.5 (Answer C) is at the bottom of the acceptable target range, making it difficult to consistently keep her INR in the range.

16. Answer: A
Anticholinergic drugs like trihexyphenidyl only control tremor, not other symptoms of Parkinson disease. Increasing the trihexyphenidyl dose (Answers B and D) would not improve control of his symptoms and would increase anticholinergic adverse effects. Decreasing the carbidopa/levodopa dose (Answer C) would worsen his Parkinson disease symptoms. Increasing the carbidopa/levodopa dose and discontinuing trihexyphenidyl (Answer A) should improve control of all of his symptoms and reduce any anticholinergic adverse effects.

17. Answer: D
Wearing-off phenomenon is the return of Parkinson disease symptoms before the next dose. This problem can be resolved by giving doses more often (Answer D), administering the controlled-release formulation of carbidopa/levodopa, or adding a catechol-*O*-methyl transferase inhibitor. Increasing the dosing interval (Answer C) means that doses are given further apart. Increasing the dose (Answer A) would not address wearing-off at the end of a dosing interval and would place the patient at risk of developing dyskinesia. Decreasing the dose (Answer B) would cause the patient's Parkinson symptoms to worsen.

18. Answer: B
Entacapone (Answer B) can cause a reddish orange discoloration of the urine. Amantadine (Answer C) can cause a reddish brown skin discoloration, but not changes in the urine. Carbidopa/levodopa (Answer A) does not cause changes in the urine. Cystitis (Answer D) is a possibility, but entacapone more likely caused the change in urine color.

19. Answer: D
Ropinirole (Answer A) helps with the initial treatment of Parkinson disease, but adding it to his current regimen without adjusting the carbidopa/levodopa dose would worsen his dyskinesia. Selegiline (Answer B) would

not address his dyskinesia and could make it worse by decreasing the breakdown of levodopa. Increasing the carbidopa/levodopa dose (Answer C) would make his dyskinesia worse. Decreasing the carbidopa/levodopa dose (Answer D) will improve the dyskinesia.

20. Answer: C
Trihexyphenidyl (Answer A) is only effective for tremors in Parkinson disease and has anticholinergic adverse effects. In this patient, it would not treat the other symptoms of the disease, and anticholinergic adverse effects are not advisable in an older individual. Rasagiline (Answer B) may slow the progression of Parkinson disease, but it does not directly treat Parkinson symptoms. Ropinirole (Answer D) is usually preferred for initial treatment in individuals younger than 65 or as add-on therapy to carbidopa/levodopa in older patients. Carbidopa/levodopa (Answer C) is the preferred initial treatment for Parkinson disease in individuals older than 65.

21. Answer: A
A β-blocker (Answer A) is a good choice for a patient with coexisting hypertension. Indomethacin (Answer B) can be used for migraine, but it is held in reserve because of serious adverse effects. Topiramate (Answer C) might decrease her weight, but it has an increased risk of teratogenic adverse effects. Sumatriptan (Answer D) is for the acute treatment of migraine headaches, not for prophylaxis.

22. Answer: C
Amitriptyline (Answer C) is effective as prophylaxis for tension headaches. Propranolol (Answer A) and topiramate (Answer B) are usually used for migraine headache prophylaxis. Rizatriptan (Answer D) is an acute treatment for migraine headaches.

23. Answer: D
Lithium (Answer D) is a prophylactic agent for cluster headaches. Atenolol (Answer A) and valproate (Answer B) are usually used for migraine headache prophylaxis. Nortriptyline (Answer C) is useful for migraine and tension headaches.

24. Answer: D
Sumatriptan (Answer D) is available as an injectable and as a nasal spray and would be appropriate to use in a patient with severe nausea and vomiting. Almotriptan (Answer A) and naratriptan (Answer B) only come in oral dosage forms and would not be optimal in the face of nausea and vomiting. Promethazine (Answer C) might reduce nausea and vomiting but would not treat the patient's migraine headache.

25. Answer: B
Topiramate (Answer D) is used as a prophylactic drug and not in the acute treatment of a migraine. Naproxen (Answer C) would be less likely to relieve her headache without being combined with a triptan. The eletriptan dose (Answer A) is the lowest dose of this drug and probably ineffective, given that she is taking the highest dose of sumatriptan. In addition, eletriptan has a short half-life, making it less effective 2 hours later. Frovatriptan (Answer B) has a longer half-life, making it more likely to prevent the headache from returning 2 hours later.

26. Answer: C
Methylprednisolone (Answer C) is the only option used for acute exacerbations. Interferon-β-1a (Answer A), glatiramer acetate (Answer B), and fingolimod (Answer D) are all used as disease-modifying therapies.

27. Answer: C
Glatiramer acetate (Answer C) is an appropriate initial choice for disease-modifying therapy. Methylprednisolone (Answer A) is only for exacerbations. Baclofen (Answer B) is only for spasticity and does not have disease-modifying properties. Providing no treatment (Answer D) would be unacceptable because of the patient's many episodes of exacerbations.

28. Answer: A
Fingolimod (Answer A) is associated with cardiac arrhythmias, and the ECG should be monitored at least every 6 months. Sodium (Answer B), pulmonary function tests (Answer C), and renal function tests (Answer D) do not need to be routinely monitored with fingolimod.

29. Answer: D
Glatiramer (Answer A) is a category B drug with limited data in pregnancy. It would be best to try an alternative agent, if possible. Mitoxantrone (Answer B) has significant toxicities and is a category X drug. Teriflunomide (Answer C) is also a category X drug.

Dimethyl fumarate (Answer D) is a pregnancy category C drug. However, this patient should carefully plan her conception and can discontinue the medication before pregnancy.

30. Answer: B

The most likely cause of peripheral neuropathy in this patient is diabetes mellitus, even if this was not previously diagnosed. Therefore, A1C (Answer B) is the most useful laboratory value for determining the potential cause. Sodium (Answer A), serum creatinine (Answer C), and white blood cell count (Answer D) do not help determine the cause of neuropathy.

31. Answer: C

Naproxen (Answer A) would unlikely be beneficial because the patient has been taking nonprescription analgesics without symptom relief. Although tramadol (Answer B) is a possibility, it is usually considered a second- or third-line option for peripheral neuropathy. Prednisone (Answer D) is not typically used for the initial treatment of neuropathy. Prednisone can be used in very specific immunologic neuropathies, but these are unlikely in this scenario. Nortriptyline (Answer C) is considered a first-line treatment for peripheral neuropathy. Given that the patient has not been previously treated, it is the best initial treatment option.

32. Answer: C

Number needed to treat (NNT) is an estimate of the number of patients who would need to receive treatment for one patient to benefit. Therefore, the lower the NNT, the more likely a treatment is to be effective. Tricyclic antidepressants, including amitriptyline (Answer C), have the lowest NNT value in this comparison, so they are most likely to be effective. Duloxetine (Answer A) and venlafaxine (Answer D) are less likely to effective. Sertraline (Answer B) is the least likely to be effective.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B
This patient most likely has focal epilepsy, given the description of his spells and the EEG. Ethosuximide (Answer A) has a very narrow spectrum of generalized nonmotor seizures, making it incorrect. Phenobarbital (Answer C) has common or severe adverse effects, making it less than optimal as initial pharmacotherapy. Clobazam (Answer D) is indicated only for Lennox-Gastaut syndrome. Levetiracetam (Answer B) is indicated for monotherapy for focal seizures and has fewer adverse effects than phenobarbital and felbamate.

2. Answer: C
With a blood glucose of less than 60 mg/dL, hypoglycemia could be a cause of this patient's status epilepticus. Although lorazepam (Answer A) and diazepam (Answer D) are appropriate for treating seizures not caused by hypoglycemia, a possible hypoglycemic episode must be treated first. Because the patient's nutritional status is unknown, she could be thiamine deficient. Giving dextrose (Answer B) in the face of thiamine deficiency could precipitate an encephalopathy. Thiamine (Answer C) should be given before dextrose.

3. Answer: A
Agitation and depression are common adverse effects of levetiracetam. Because of the patient's wife's concerns for his irritability and depression, it is probably advisable to discontinue levetiracetam (Answer A) and change to a different ASM. Increasing the dose (Answer B) could worsen his symptoms, and his symptoms are probably not the result of ongoing seizures. Continuing levetiracetam (Answer C) might be an alternative, but given that he and his spouse have concerns for adverse effects, it is a less-than-optimal approach. No clear correlation has been established between efficacy or toxicity and levetiracetam concentrations (Answer D). Therefore, a concentration would not help guide therapeutic decisions.

4. Answer: B
The most critical test before initiating treatment for stroke is head imaging. A CT scan of the head (Answer B) allows the clinician to distinguish between an ischemic stroke and a hemorrhagic stroke. A cerebral angiogram (Answer A) may be helpful later to determine whether there is a lesion in the cerebral vasculature, but it is not essential in the acute setting. A coagulation panel (Answer C) is not necessary to determine whether to initiate alteplase in the acute setting. Similarly, an echocardiogram (Answer D) may be useful in a patient's diagnostic workup after a stroke, but it is not necessary in the acute care setting.

5. Answer: A
A combination of aspirin and clopidogrel is indicated for 90 days after an ischemic stroke (Answer A). A combination of aspirin and dipyridamole (Answer B) is a possible option for long-term stroke prophylaxis, but this combination is more effective in the first 90 days after a stroke. Apixaban (Answer C) is only indicated for prophylaxis in the setting of atrial fibrillation, which this patient does not have. Warfarin (Answer D) is only indicated for prophylaxis of stroke in atrial fibrillation or mechanical mitral valve replacement.

6. Answer: D
Gait disturbances (Answer A), falls (Answer B), and handwriting (Answer C) are not improved by use of levodopa or a dopamine agonist. Rigidity (Answer D) is improved with levodopa or a dopamine agonist.

7. Answer: B
This patient is experiencing wearing-off before the next dose. A catechol-O-methyl transferase inhibitor, entacapone (Answer B), slows the degradation of dopamine in the synaptic cleft and extends the effectiveness of levodopa. Rasagiline (Answer A) is a selective MAO inhibitor that may be used to slow the progression of Parkinson disease. Apomorphine (Answer C) is indicated for on-off phenomenon but is not indicated for wearing-off before the next dose. Quetiapine (Answer D) is a preferred antipsychotic to manage hallucinations and psychiatric adverse effects of levodopa.

8. Answer: D
Many medications used for nausea, including metoclopramide (Answer B) and promethazine (Answer A), are dopamine antagonists and potentially worsen nausea and vomiting. Reducing carbidopa/levodopa (Answer C) would likely worsen Parkinson symptoms. Trimethobenzamide (Answer D) is a selective antagonist for the D_2 receptor, making it less likely to worsen Parkinson symptoms.

9. Answer: A
This patient most likely has tension headaches, given his description of the headaches. The most effective medication for acute treatment of tension headaches is naproxen (Answer A). Sumatriptan (Answer B) and dihydroergotamine (Answer C) are indicated for acute treatment of migraine-type headaches. Lithium (Answer D) is only used to prevent cluster headaches.

10. Answer: A
This patient most likely has a tension-type headache. Amitriptyline (Answer A) is effective for preventing tension-type headaches. Valproate (Answer B) and topiramate (Answer C) are not used to prevent tension-type headaches. Frovatriptan (Answer D) is only indicated for the acute treatment of migraine.

11. Answer: D
Fingolimod (Answer D) is the only choice with an FDA indication for the treatment of MS. In addition, fingolimod has the best clinical trial evidence of efficacy. Methylprednisolone (Answer B) is used for acute MS exacerbations. Cyclophosphamide (Answer A) and azathioprine (Answer C) have been studied in progressive forms of MS, but their data are not as robust as those for fingolimod.

12. Answer: B
Treatment of spasticity in MS requires a centrally acting agent. Of the choices given, only diazepam (Answer A) and baclofen (Answer B) are centrally acting. Because of the significant fatigue and drowsiness that occur with diazepam, baclofen is usually a first-line therapy. Carisoprodol (Answer C) and metaxalone (Answer D) are indicated for muscle spasms, but not for spasticity.

13. Answer: C
Amantadine (Answer C) is used in MS for fatigue. Propranolol (Answer A), lamotrigine (Answer B), and ropinirole (Answer D) are not used in MS.

14. Answer: A
Diabetic neuropathy (Answer A) is the most common cause of peripheral neuropathy and may occur even before a patient is given a diagnosis of diabetes. Chronic inflammatory demyelinating polyneuropathy (Answer B) and genetic neuropathy (Answer D) are much less common, and symptoms are not consistent with this presentation. An entrapped nerve (Answer C) would typically be unilateral.

15. Answer: B
Carbamazepine (Answer A) and valproate (Answer D) are considered third- or fourth-line drugs for diabetic neuropathy pain. Acetaminophen (Answer C) would unlikely relieve symptoms. Lidocaine (Answer B) would be best for initial treatment of the patient's neuropathic pain.